FORMULATION AND EVALUATION OF ANTI-DIABETIC INLAY TABLETS

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the requirement for the award of the degree of

MASTER OF PHARMACY

(PHARMACEUTICS)

Submitted By

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Under the guidance of

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MAY - 2012

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CERTIFICATE

This is to certify that the work embodied in this thesis entitled **"FORMULATION AND EVALUATION OF ANTI-DIABETIC INLAY TABLETS"** submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai, was carried out by **Ms. REEPA PATEL.K** (Reg.No.26104207) in the Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 in partial fulfillment for the degree of **MASTER OF PHARMACY** in Pharmaceutics under my direct supervision and guidance.

This work is original and has not been submitted in part or full for any other degree or diploma of any university.

Place: Erode **Dr. S. TAMIZHARASI, M.Pharm., Ph.D.**

Date: Research Guide

EVALUATION CERTIFICATE

This is to certify that the work embodied in this thesis entitled, **"FORMULATION AND EVALUATION OF ANTI-DIABETIC INLAY TABLETS"** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, was carried out by Reg. No. **26104207** in the Department of Pharmaceutics, Nandha College of Pharmacy and Research institute, Erode-52 for the partial fulfillment for the award of degree of **MASTER OF PHARMACY** in Pharmaceutics under the supervision and guidance of **Dr.S.THAMIZARASI, M.Pharm., PhD.,** Head of the department, Department of Pharmaceutics, Nandha College of Pharmacy and Research Institute, Erode- 52.

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DECLARATION

The work presented in this thesis entitled **"FORMULATION AND EVALUATION OF ANTI-DIABETIC INLAY TABLETS"** was carried out by me in the Department of Pharmaceutics, Nandha College of Pharmacy, Erode, under the direct supervision and guidance of **Dr. S. TAMIZHARASI M.Pharm., Ph.D.,** Nandha College of Pharmacy, Erode -52.

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LIST OF ABBREVIATIONS

%	-	percentage
Kg	–	kilogram
Gm	–	gram
Mg	–	milligram
µg	–	microgram
ml	–	millilitre
°C	–	centigrade
Nm	–	nanometer
µl	–	microliter
CI	–	carr's index
Mm	–	millimetre
HPLC	–	high performance liquid chromatography
UV	–	ultra-violet spectrophotometer
HPMC	–	hydroxypropyl methyl cellulose
MCCP	–	micro crystalline cellulose powder
SSG	-	sodium starch glycholate
Mins	–	minutes
RH	–	relative humidity
USP	–	united states pharmacopoeia
NF	–	national formulary
BP	–	british pharmacopoeia

ICH	–	international conference on harmonisation
#	-	mesh
SD	–	standard deviation
Abs	–	absorbance
IR	–	immediate release
SR	–	sustained release
Cm	–	centimetre
Con	–	concentration
F	-	formulation

1. INTRODUCTION

1.1.TABLETS [1]:

Tablets are defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared by either compression or molding methods. Tablets remain popular because of the advantages afforded both to the manufacturer (eg: simplicity and economy of preparation, stability and convenience in packaging, shipping and dispensing) and the patient (eg: accuracy of dosage, compactness, portability). They vary in shape, size and weight depending upon the amount of drug substance present and the intended method of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablets.

Advantages of tablets:

1. They are a unit dose form, and they offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
2. Their cost is lowest of all oral dosage forms.
3. They are the lightest and most compact of all oral dosage forms.
4. They are in general the easiest and cheapest to package and ship of all oral dosage forms.
5. Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
6. They may provide greatest ease of swallowing with the least tendency for hang-up above the stomach, especially when coated, provided that tablet disintegration is not excessively rapid.
7. They lend themselves to certain special release profile products, such as enteric or delayed-release products.
8. They are better suited to large-scale production than other unit oral dosage forms.
9. They have the best combined properties of chemical, mechanical, microbiologic stability of all the oral forms.

Disadvantages of tablets:

1. They are difficult to swallow in case of paediatric, geriatric, unconscious patients.
2. Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low density character.
3. Drugs with poor wetting, sloe dissolution properties, optimum absorption or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.
4. Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or coating.

Types of Tablets:

Tablets are mainly classified into 4 categories according to their route of administration. The following are the 4 groups.

I. Oral tablets for ingestion

a. Standard compressed tablets
b. Multiple compressed tablets
    - Compression coated tablet
    - Layered tablet
    - Inlay tablet
c. Modified Release tablet
d. Delayed action tablet
e. Targeted tablet
    - Floating tablet
    - Colon targeting tablet
f. Chewable tablet
g. Dispersible tablet

II. Tablets used in the oral cavity

a. Lozenges and troches
b. Sublingual tablet
c. Buccal tablet
d. Dental cones

e. Mouth dissolved tablet

III. Tablets administered by other routes

a. Vaginal tablet

b. Implants

IV. Tablets used to prepare solution

a. Effervescent tablet

b. Hypodermic tablet

c. Soluble tablet

With advancement in technology and increase in awareness towards modification in standard tablet to achieve better acceptability as well as bioavailability, newer and more efficient tablet dosage form are developed.

I. Bilayer tablet
II. Multilayer tablet
III. Inlayer tablet
IV. Inlay tablet

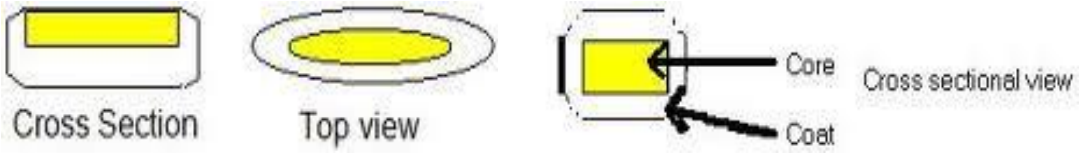
1.2.INLAY TABLETS [2]:

A variation of the compression coated tablet is the inlay tablet. In the inlay tablet, instead of the core tablet being completely surrounded by the coating, its top surface is completely exposed i.e., only the bottom layer of the coating is deposited in the die and core is placed on it. It is a dosage form comprising of high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release high dose high solubility active ingredient per unit is from 500 mg to 1500 mg and the weight of immediate release active ingredient is up to 50 mg.

The dosage form consists of two parts, core portion as an immediate release and cup portion as modified release.

- The core portion consists of super disintegrant, low dose drug and excipients.
- The cup portion consists of high dose, high solubility active ingredient, hydrophilic release controlling agent and excipients

Fig No.1 Inlay Tablets



Advantages of inlay tablets over compression coated and layered tablets:

1. It requires less coating material.
2. Core is visible so core less tablets are easily detected.
3. The reduction in the amount of coating makes for a thinner tablet.
4. It effectively avoids the problem of separation of layers of multi-layered tablets.
5. It gives accurate dosing and is prepared by conventional and simple process.
6. It further teaches the use of hydrophilic release controlling agents which do not hinder the release of immediate release active ingredient.
7. Freedom from capping of top coating.

1.3.Immediate release tablets [3]:

Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates. Immediate release dosage forms are those for which ≥85% of labelled amount dissolves within 30 min. For immediate release tablets, the only barrier to drug release is simple disintegration or erosion stage, which is generally accomplished in less than one hour1. To enhance dissolution and hence bioavailability of any drug from immediate release tablets, disintegration is one of the important process. Few Super-disintegrants are available commercially as Croscarmellose sodium, Crospovidone and SSG.

Super disintegrants play a major role in the disintegration and dissolution of MDT. Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation which forms a porous structure. The optimum concentration of the superdisintegrant can be selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrant, whereas if concentration of superdisintegrant is above critical concentration, the disintegration time remains almost constant or even increases.

1.4.Sustained release dosage form [4]:

Conventional drug delivery systems are used in treatment of an acute disease or a chronic disease using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectables as drug carriers. This type of drug delivery system is known to provide a prompt release of drug. Therefore, to achieve as well as to maintain the drug concentration within therapeutically effective range needed for treatment, it is often necessary to take this type of delivery system several times a day. This results in significant fluctuations in drug levels.

To avoid the above disadvantage several techniques have been developed which are capable of controlling the rate of drug delivery, sustaining duration of therapeutic activity, and/or targeting the delivery of drug to tissue.

Sustained release can be described as a pharmaceutical dosage form formulated to retard the release of therapeutic agent such that its appearance in systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration.

Advantages of sustained release drug delivery system:

1. Reduction in dosing frequency.
2. Reduced fluctuations in circulating drug levels.
3. Avoidance of night time dosing.
4. Increased patient compliance.
5. More uniform effect.
6. Decreased side effects like reduced GI irritation.

1.5.DIABETES MELLITUS:

Diabetes mellitus, often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced.

Signs and symptoms:

The classical symptoms of diabetes are

- polyuria (frequent urination)
- polydipsia (increased thirst)
- polyphagia (increased hunger)
- blurred vision
- diabetic dermadromes (skin rashes)

Causes:

Insulin is a hormone produced by the pancreas to control blood sugar. Diabetes can be caused by too little insulin, resistance to insulin, or both. This is because:

- The pancreas does not produce enough insulin.
- The muscle, fat, and liver cells do not respond to insulin normally.
- Both of the above.

Diagnosis:

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:

The cut off samples of venous plasma samples are:

Fasting blood sugar = 126 mg/dl (after minimum 8 hrs of fasting)

Random blood sugar = 200 mg/dl (sample taken at any time of the day)

Post prandial blood sugar = 200 mg/dl (2 hrs postprandial state)

Oral glucose tolerance test is the gold standard for diagnosis.

Categorizing diabetes mellitus:

There are three major types of diabetes:

Type 1 diabetes is usually diagnosed in childhood. Many patients are diagnosed when they are older than age 20. The body makes little or no insulin. Daily injections of insulin are needed. The exact cause is unknown. Genetics, viruses and autoimmune problems play a major role.

Type 2 diabetes is far more common than type 1. It makes up most of diabetes cases. It usually occurs in adulthood, but young people are increasingly being diagnosed with this disease. The pancreas does not make enough insulin to keep blood glucose levels normal,

often because the body does not respond well to insulin. Many people with type 2 diabetes do not know they have it, although it is a serious condition. Type 2 diabetes is becoming more common due to increasing obesity and failure to exercise.

Gestational diabetes is high blood glucose that develops at any time during pregnancy in a woman who does not have diabetes.

2. LITERATURE REVIEW

Kotta Kranthi Kumar et al [5]., Reported that Bilayer tablets of Metformin Hydrochloride and gliclazide was successfully formulated and evaluated. The investigation was aimed to the development of bilayered tablets of metformin hydrochloride and gliclazide as sustained release by using HPMC as retardant. The best formula was selected by physical evaluation of tablets, comparative dissolution profiles and similarity factor correlation studies of various formulations of metformin hydrochloride and gliclazide.

N. N. Rajendran et al [6]., Concluded that Bilayer tablets of Pioglitazone HCl and Metformin HCl as an alternative to the conventional dosage form. Sustained layer of metformin were prepared by wet granulation method using different viscosity grade of HPMC as polymers and immediate release layer were prepared by direct compression using superdisindegrants such as SSG and crosscarmellose sodium. The result showed that combinations of polymers HPMC K100M and HPMCK4M in sustained layer can control the release of drug.

AR Mullaicharam et al [7]., Developed once daily sustained release matrix tablets of metoprolol tartrate with inlay hydrochlorthiazide tablet as immediate release. Both the layers were prepared by wet granulation method. Five trial batches of sustained release granules were prepared using HPMC in various percentages and one optimum formulation was selected among them on basis of in vitro dissolution studies.

Yamsani Madhusudan Rao et al [8]., Reported that formulated bilayer tablets provided immediate release of glimepiride and metformin HCl as sustained release over a period of 8 hours.The immediate release layer was prepared using sodium starch glycolate as super disintegrant and sustained release using HPMC K4M and sodium carboxy methyl cellulose as polymers and PVP K30 as binder. Formulation containing higher concentration of sodium starch glycolate and SCMC in IR and SR layer respectively were optimised for bilayer tablets.

Manoranjan Sahu et al [9]., Concluded that modified inlayered tablet containing glimepiride as immediate release and metformin as sustained release was designed to improve oral therapeutic efficacy. Tablet compressing was done with core rod tooling where only one surface of core is exposed to outside and other drug is incorporated in cup

portion. Common analytical method was developed for quantitative combined drug estimation.

Laxmi Goswami et al [10]., Concluded that formulated floating bilayer tablets of metformin and pioglitazone remain buoyant over a period of 12-20 hours and released more than 80% of drug. The tablets were formulated by modified direct compression using polymers like HPMC, carbopol, PVP to facilitate immediate release of pioglitazone and sustained release of metformin and were subjected to various evaluation parameters including floating lag time, floating duration, drug content and spectrophotometric simultaneous estimation.

J. Bagyalakshmi et al [11]., Reported that bilayer matrix tablet containing 500mg of metformin HCl as SR from one layer and 5mg glipizide as IR from another layer can be prepared by solid dispersion method. Solubilty of glipizide was increased by solid dispersion technique with sodium starch glycolate using kneading technique. Metformin was formulated using different grades of HPMC.

Chitra. P et al [12]., Formulated and optimized once daily sustained release inlay tablet of propranolol hydrochloride and hydrochlorthiazide.SR active ingredient is selected from higher dose and IR active ingredient is selected from lower dose. Tablets were evaluated for hardness, thickness, uniformity of weight, friability, content uniformity, in-vitro drug release. Optimized formulation could extend release of PRO for 24 hrs and HCTZ for 15 mins.

Tapan Kumar Pal et al [13]., Concluded that the study helped in finding optimum formulation of Metformin HCl with sustained drug release. Tablets were prepared by non-aqueous wet granulation method using HPMC K15M as matrix forming polymer. Drug release profile was formulated using response surface methodology. Indepependant variables were HPMC K15M and PVP K30 whereas dependant variables were % of drug released in 1hr, 8 hrs and time to 50% drug release.

Sahu Manoranjan [14]., Reported that the designed inlayered tablet of glimepiride as immediate release and metformin hydrochloride as sustained release indicated suitability for patient compliance. Inner core portion was desingned using superdisintegrants for immediate release and outer cup portion was designed using polymers such as HPMC and PVP to modulate drug release.

P. Jeyaprabha et al [15]., Prepared a modified release tablet of gliclazide by using different grades of hydroxypropyl cellulose. Release process involved erosion and diffusion mechanism. Among all the 9 formulations prepared, formulation F9 with GXF 15% cum EXF 12% had good release and highest f2 (56.9) value, therefore it was decided to comparable with innovator F1.

Poonam S. Karekar et al [16]., Proposed spectrophotometric method for the estimation gliclazide in bulk and pharmaceutical dosage form. Wavelength maxima for gliclazide was found to be 229.5nm with molar absorptivity of 1.4962×10^4l/mol/cm. Beer's law was obeyed in the concentration range of 7-27 µg/ml. The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.31µg/ml and 0.92 µg/ml. Percentage recovery of drug for the proposed method ranged from 98.68-100.12% indicating no interference of the tablet excipients.

Tanbir Ahammad et al [17]., Prepared matrix tablets of gliclazide by direct compression and wet granulation process using Methocel K15M CR, studied effect of granulation process on drug release and found that wet granulation extend release more than that of direct compression technique.

Shinde Anilkumar J et al [18]., Prepared fast dissolving tablets of gliclazide by direct compression method using superdisintegrants crosspovidone and croscarmellose sodium with binders PVP K30 and pregelatinised starch and concluded that Croscarmellose sodium was best superdisintegrant with PVP K30 as binding agent showing more than 99% of drug release within 12 minutes.

Chauhan Pratik Navinchandra et al [19]., Developed mouth dissolving tablets of gliclazide using three super disintegrants hypromellose, crosspovidone and sodium starch glycolate at different concentrations with microcrystalline by direct compression. Among all the twelve formulations crosspovidone F6 emerged as overall best formulation due to its fast invitro dispersion when compared to other formulations and 97% drug release within 15 min.

Raja Rajeswari K et al [20]., Developed modified release hydrogel formulations of a poorly soluble drug, Gliclazide using a hydrophilic polymer HPMC in two grades i.e., HPMC 15cps and Methocel K4M. All six formulations were developed and evaluated for invitro drug release upto 16hrs and compared with that of marketed formulation. GMF VI

was found to have similar release pattern proving to show controlled release following zero order release by anomalous diffusion.

S. Chandra et al [21]., Prepared fast dissolving tablets of gliclazide using solid dispersion and various concentrations of superdisintegrant agents like Ac-Di-Sol, Crospovidone, sodium starch glycolate by direct compression method. Among nine formulations, tablets of batch F6 containing Crospovidone and Avicel 102 showed super organoleptic properties along excellent invitro disintegration time and drug release as compare to other formulations.

Mahendra labana et al [22]., Designed modified release gliclazide by direct compression using HPMC as polymer, Dibasic calcium phosphate and maltodextrin as binder. The prepared formulations were further evaluated for hardness, friability, drug content uniformity, in vitro dissolution time and short term stability and drug excipient interaction were studied.

Narendra Sharma et al [23]., Developed second derivative spectrophotometric method for determination of metformin hydrochloride in bulk and in tablet dosage form. The quantitative determination of the drug was carried out using the second derivative values measured at 233.8 nm. Calibration graph constructed at 233.8 nm was linear in concentration range of 4-20 μg/ml with correlation coefficient 0.9979. The method was validated as per ICH guidelines and can be used for determination of Metformin hydrochloride in tablet dosage form.

S A Patil et al [24]., Formulated solid dispersion of metformin hydrochloride using methocel K100M as carrier by solvent evaporation and cogrinding method. Solid dispersion with 1:4 and 1:5 ratio of drug to polymer obtained by solvent evaporation and cogrinding were selected as best candidates suitable for prolonged release oral dosage form of metformin.

Dr K.L.Senthilkumar et al [25]., Formulated and evaluated metformin sustain release tablets using different polymers as release retarding agent and concluded that formulation of sustained release tablet of metformin containing 13% HPMC K100 with binder PVP K30 was found to be ideal or optimized formulation of sustained release tablets for 10 hour release as it fulfils all the requirements for sustained release tablet.

M. M. Varma et al [26]., Designed gastroretentive floating drug delivery system of metformin hydrochloride using HPMC K4M and carbopol 934P as polymers and sodium bicarbonate as gas generating agent by wet granulation method. Release of metformin HCl from the floating tablets formulated with HPMC and /carbopol was slow and spread over 12 h and depended on % of polymer in the tablet. Batch F4 (carbopol 934P 150 mg, sodium bicarbonate 50 mg) showed better sustained release than other formulations.

N. Aruna et al [27]., Formulated metformin HCl sustained release matrix tablet using Syzygium cumini as a release retarding agent which is antidiabetic in nature using various polymers HPMC K100M, Eudragit RLPO, Carbopol940, Ethyl cellulose by wet granulation method. Formulation containing HPMC K100M and ethyl cellulose showed sustained drug release pattern upto 12 hrs which matched drug release pattern of innovator.

Sunil Kumar et al [28]., Designed extended release metformin tablet by wet granulation method using HPMC K100M as polymer, stearic acid and IPA as binder. The prepared formulations were further evaluated for hardness, friability, drug content uniformity, in vitro dissolution time and for in vitro drug release pattern in pH 6.8 phosphate buffer and short term stability and drug-excipient interaction were studied.

Manju Nagpal et al [29]., Developed oro-dispersible tablets of metformin by direct compression method using super disintegrants, effervescent and sublimation approach. Batch C4 prepared by effervescent approach was found to have the least disintegration time and maximum in vitro dissolution profile.

Margret Chandira et al [30]., Formulated extended release matrix tablet of metformin hydrochloride using different combinations of polymers HPMC K100M CR and carbopol 71 G by wet granulation method. Formulations F7, F9 and F10 containing HPMC K 100 M CR and Carbopol 71G in different concentration shows the extended drug release for up to 10 hrs, among these formulation, F10 is considered as optimized formulation because it shows similar drug release pattern with that of innovator.

Harrower AD et al [31]., Performed studies to assess the efficacy of various sulfonyl ureas in the management of diet failed NIDDM patients. The results showed that gliclazide is a potent hypoglycaemic agent having low incidence of side effects, few problems with hypoglycaemia and retains its efficacy longer than other sulfonylureas.

Pareek et al [32]., Evaluated efficacy and tolerability of gliclazide and metformin combination and found that addition of gliclazide to metformin is an effective treatment for inadequately controlled patients on sulfonyl urea or metformin alone and its combination achieves good glycemic control and improves lipid levels with better tolerability.

3. AIM AND OBJECTIVE

To provide effective, safe and stable pharmaceutical oral formulation of inlay tablet containing both immediate release and sustained release of two antidiabetic drugs with different mechanisms of action to improve glycemic control.

Diabetes a global public health problem is a chronic disease and is now growing as an epidemic in both developed and developing countries. It occurs in two forms Type I and Type II. Type II is more common which can be treated by giving insulin or oral hypoglycemic agents. Upon progression of the disease, progressive loss of β-cell function and mass makes it difficult for patients to maintain glycemic control with monotherapy. As a result, combination therapy involving agents with complementary mechanism of action is the next logical step in the management of T2DM.

Metformin hydrochloride (MH), is the first choice of drug among all the oral hypoglycemic patients as it lowers both basal- and postprandial-elevated blood glucose in patients with non-insulin-dependent diabetes mellitus, does not lead to weight gain and has been shown to possess lipid-lowering properties. Since metformin lowers plasma glucose without affecting insulin secretion, it is often combined with an agent stimulating insulin secretion, like a sulfonylurea. Adding a sulfonylurea to metformin has thus been the conventional and the gold standard combination therapy for decades. Gliclazide is the first choice among all the sulfonyl urea because of its low incidence of side effects and secondary failure, few problems with hypoglycaemia.

Metformin HCl is formulated as sustained release because gastrointestinal absorption of metformin is incomplete with an absolute bioavailability of 40–60% (under fasting conditions) in combination with rapid elimination and 20–30% of an oral dose is recovered in faeces. Side effects and the need for twice to three times a day administration when larger doses are required can also reduce patient compliance. Therefore due to all the above drawbacks it is necessary to formulate Metformin HCl as SR to reduce dosing frequency and improve patient compliance.

Gliclazide is formulated as immediate release using super disintegrant as it has very long half life of 6-8 hrs to increase insulin secretion as soon as it is administered.

4. PLAN OF WORK

- Raw material analysis
- Preformulation studies

  Melting point determination of active ingredients

  Determination of λ_{max}

  Drug-Excipient Physical compatability studies

  Chemical compatability studies – by FTIR

  Calibration curve

- Formulation of sustained release tablets

  By using different polymers with different concentrations

  Pre compression study of tablet

  Post compression study of tablets

- Formulation of immediate release tablets

  By using different concentrations of disintegrants

  Pre compression study of tablet

  Post compression study of tablet

- Optimization of formulation with respect to in vitro release profile of SR and IR tablets
- Formulation of Inlay tablets
- Evaluation of Inlay tablets
- Evaluation of Swelling and Erosion behaviour of the Inlay tablets
- Determination of in vitro release kinetic studies for the Inlay tablets.
- Determination of stability of Inlay tablets as per ICH Guidelines.

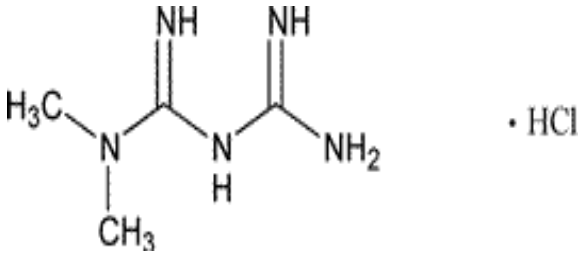
5. DRUG PROFILE

METFORMIN HYDROCHLORIDE:

Metformin is an oral antidiabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function.

Chemical structure:

Fig No. 2. Structure of Metformin HCl



IUPAC name: N,N-dimethylimidodicarbonimidic diamide

Chemical formula: $C_4H_{11}N_5$.HCl

Molecular weight: 165.63 g/mol

Category : hypoglycemic

Dose : 0.5 to 3 g daily, in divided doses

PROPERTIES:

Description : white, crystalline powder hygroscopic

Solubility : freely soluble in water; slightly soluble in ethanol (95%); practically insoluble in acetone, chloroform, dichloromethane and ether.

Melting point : 222-226˚C

Storage : store in well closed container.

Mechanism of action:

Metformin improves hyperglycemia primarily by suppressing glucose production by the liver. Metformin activates AMP-activated protein kinase (AMPK), an enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats. The mechanism by which biguanides increase the activity of AMPK remains uncertain; however, metformin increases the amount of cytosolic AMP. In addition to suppressing hepatic glucose production, metformin increases insulin sensitivity, enhances peripheral glucose uptake (by phosphorylating GLUT-4 enhancer factor), increases fatty acid oxidation and decreases absorption of glucose from the gastrointestinal tract. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors.

Bioavailability : 50 to 60% under fasting conditions

Half life : 6.2 hours

Plasma protein binding : negligible

Volume of distribution : 300 – 1000 L

Metabolism : none.

Excretion : active renal tubular excretion.

CONTRAINDICATIONS

Hypersensitivity to drug.

Acute or chronic metabolic acidosis with or without coma.

Underlying renal dysfunction.

Heart failure requiring drug therapy.

ADMINISTRATION

- Administer with a meal.
- Make sure patient swallows extended release tablets whole without crushing or chewing.
- Don’t administer extended release tablets to children.

DOSING INFORMATION

- Usual Adult Metformin Dose for Diabetes Mellitus Type II:

  500 mg orally twice a day (with the morning and evening meal)

- Extended Release:

  500 to 2000 mg orally once a day (with the evening meal). Maximum daily dose is 2500 mg.

ADVERSE REACTIONS

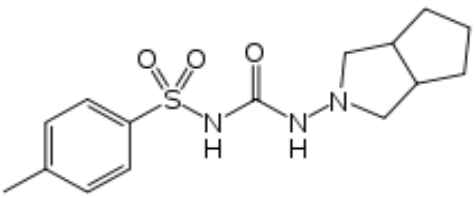
Diarrhea, nausea, vomiting, abdominal bloating, abdominal cramping or pain, flatulence, anorexia.

GLICLAZIDE:

Gliclazide is an oral hypoglycemic and is classified as a sulfonylurea.

Structure:

Fig No. 3 Structure of Gliclazide



IUPAC name : N-(hexahydrocyclopenta[c]pyrrol-2(1H)-ylcarbamoyl)-4 methylbenzenesulfonamide.

Molecular weight : 323.412 g/mol

Molecular formula : $C_{15}H_{21}N_3O_3S$

Pharmacologic class : sulfonyl urea

Therapeutic class : hypoglycemic

Dose : 40- 320 mg daily, doses >160 mg daily may be given in 2 divided doses.
Modified release tablets 30-120 mg daily.

PROPERTIES:

Description : White, hydrophobic powder

Solubility : Slightly soluble in water and soluble in methanol

Melting point : 181^0C

Storage : store in well closed container.

Mechanism of action:

Gliclazide selectively binds to sulfonylurea receptors (SUR-1) on the surface of the pancreatic beta-cells. It was shown to provide cardiovascular protection as it does not bind to sulfonylurea receptors (SUR-2A) in the heart. This binding effectively closes the K+ ion channels. This decreases the efflux of potassium from the cell which leads to the depolarization of the cell. This causes voltage dependent Ca++ ion channels to open increasing the Ca++ influx. The calcium can then bind to and activate calmodulin which in turn leads to exocystosis of insulin vesicles leading to insulin release.

Half life : 10.4 hours

Plasma protein binding : 94%, highly bound to plasma proteins

Metabolism : Extensively metabolized in the liver

Excretion : Metabolites and conjugates are eliminated primarily by the kidneys (60-70%) and also in the feces (10-20%).

Indications :

Gliclazide is used for control of hyperglycemia in gliclazide-responsive diabetes mellitus of stable, mild, non-ketosis prone, type 2 diabetes. It is used when diabetes cannot be controlled by proper dietary management and exercise or when insulin therapy is not appropriate.

Contraindications

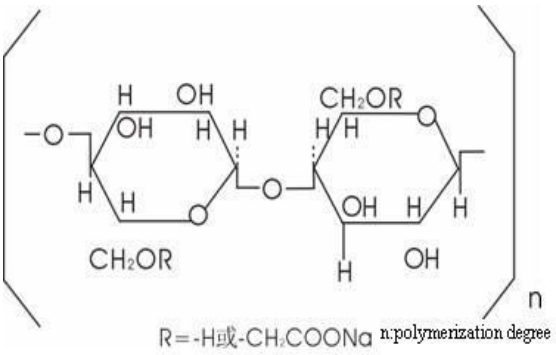
- Type 1 diabetes
- Hypersensitivity to sulfonylureas
- Severe renal or hepatic failure
- Pregnancy and lactation
- Miconazole coprescription

Adverse effects:

- Hypoglycemia - while it was proven to have the same efficacy as glimepiride, one of the newer sulfonylureas, the European GUIDE study has shown that it has approximately 50% fewer confirmed hypoglycaemic episodes in comparison with glimepiride.
- Gastrointestinal disturbance (reported)
- Skin reactions (rare)
- Hematological disorders (rare)
- Hepatic enzyme rises (exceptional)

SODIUM STARCH GLYCOLATE [40] :

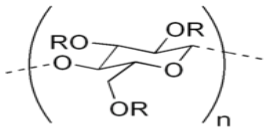
1. **Nonproprietary Names :**
   BP : Sodium Starch Glycollate
   Ph Eur : Carboxymethylamylum natricum
   USPNF : Sodium starch glycolate
2. **Synonyms :**
   Carboxymethyl starch, sodium salt; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.
3. **Chemical Name :**
   Sodium carboxymethyl starch.
4. **Structural Formula :**



5. **Molecular weight :**
   $5\times10^5 - 1\times10^6$
6. **Functional Category :**
   Tablet and capsule disintegrant
7. **Applications in pharmaceutical formulation or technology :**
   Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.
   Sodium starch glycolate has also been investigated for use as a suspending vehicle.
8. **Description :**
   Sodium starch glycolate is a white to off-white, odourless, tasteless, free-flowing powder.
9. **Typical Proprties :**
   Acidity / alkalinity : pH 3.0–5.0 or pH 5.5–7.5 for a 3.3% w/v aqueous dispersion.

CROSCARMELLOSE SODIUM [40]:

1. **Nonproprietary Names :**
   BP : Croscarmellose sodium
   PhEur : Carmellosum natrium conexum
   USPNF : Croscarmellose sodium
2. **Synonyms :**
   Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.
3. **Chemical Name :**
   Cellulose, carboxymethyl ether, sodium salt, crosslinked
4. **Empirical Formula :**
   Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium.
5. **Structural Formula :**

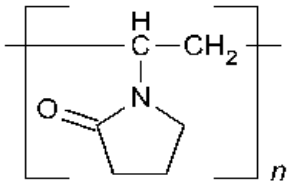


R = H or CH_2CO_2H

6. **Molecular weight :**
   90 000–700 000.
7. **Functional category :**
   Tablet and capsule disintegrant.
8. **Applications in pharmaceutical formulation or technology :**
   Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets. In tablet formulation croscarmellose sodium may be used in both direct-compression and wet-granulation processes.
   When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.
9. **Description :**
   Croscarmellose sodium occurs as an odorless, white or grayish white powder.
10. **Typical properties :**
    Acidity/alkalinity: pH = 5.0–7.0 in aqueous dispersions.
    Density (bulk) : 0.529 g/cm3 for Ac-Di-Sol
    Density (tapped) : 0.819 g/cm3 for Ac-Di-Sol
    Density (true) : 1.543 g/cm3 for Ac-Di-Sol
    Solubility : insoluble in water, although croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

CROSPOVIDONE [40] :

1. **Nonproprietary Names :**
   BP : Crospovidone
   PhEur : Crospovidonum
   USPNF: Crospovidone
2. **Synonyms :**
   Crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.
3. **Chemical Name :**
   1-Ethenyl-2-pyrrolidinone homopolymer
4. **Empirical Formula :**
   The USPNF 23 describes crospovidone as a water-insoluble synthetic crosslinked homopolymer of N-vinyl-2-pyrrolidinone.
5. **Structural Formula :**



6. **Molecular weight :**
   (C6H9NO)n >1 000 000
7. **Functional Category :**
   Tablet disintegrant.
8. **Applications in pharmaceutical formulation or technology :**
   Crospovidone is a tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels.
   Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs.
9. **Description :**
   Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.
10. **Typical properties :**
    Acidity/alkalinity : pH 5.0–8.0 (1% w/v aqueous slurry)
    Density : 1.22 g/cm3
    Solubility : Practically insoluble in water and most common organic solvents.

XANTHAN GUM [40]:

1. **Nonproprietary Names :**

   BP: Xanthan gum

   PhEur: Xanthani gummi

   USPNF: Xanthan gum

2. **Synonyms :**

   Corn sugar gum; E415; Keltrol; polysaccharide B-1459; Rhodigel; Vanzan NF; Xantural

3. **Chemical Name :**

   Xanthan gum.

4. **Functional Category :**

   Stabilizing agent; suspending agent; viscosity-increasing agent.

5. **Applications in pharmaceutical formulation or technology :**

   Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent.(3–5) It is also used as a thickening and emulsifying agent.

6. **Description :**

   Xanthan gum occurs as a cream- or white-colored, odorless, free-flowing, fine powder.

7. **Typical properties :**

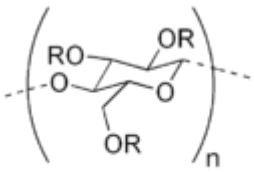
   Acidity/alkalinity: pH = 6.0–8.0 for a 1% w/v aqueous solution.

   Melting point : chars at 270˚C.

   Solubility : practically insoluble in ethanol and ether; soluble in cold or warm water

HYDROXY PROPYL METHYL CELLULOSE [40]:

1. **Nonproprietary Names :**
   BP: Hypromellose
   JP: Hydroxypropylmethylcellulose
   PhEur: Hypromellosum
   USP: Hypromellose
2. **Synonyms :**
   Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.
3. **Chemical Name :**
   Cellulose hydroxypropyl methyl ether
4. **Structural Formula :**



R = H or CH_3 or $CH_2CH(OH)CH_3$

5. **Functional Category :**
   Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; tablet binder; viscosity increasing agent.
6. **Applications in pharmaceutical formulation or technology :**
   Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.
   Oral use - tablet binder, in film-coating, and as a matrix for use in Extended - release tablet formulations.
   Ophthalmic use - added as a thickening agent to vehicles for eye drops and artificial tear solutions.
   Topical use - emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.
7. **Description :**
   Hypromellose is an odorless and tasteless, white or creamywhite fibrous or granular powder.
8. **Typical Properties :**
   Acidity/alkalinity : pH = 5.5–8.0 for a 1% w/w aqueous solution.
   Density (tapped) : 0.557 g/cm3
   Density (true) : 1.326 g/cm3
   Solubility : soluble in cold water, forming a viscous colloidal solution

9. Viscosity (dynamic):

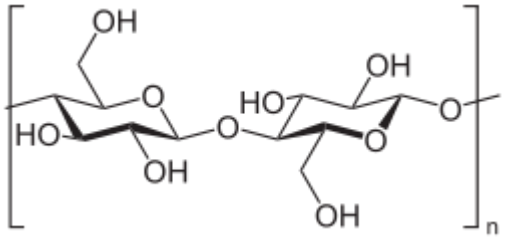
A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared.

Typical viscosity values for 2% (w/v) aqueous solutions of methocel (Dow Chemical Co.) viscosities measured at 20ºC

Methocel grade	Viscosity(cps)
K4 M	4000
K15M	15000
K100M	100000

MICRO CRYSTALLINE CELLULOSE [40] :

1. **Nonproprietary Names:**
   BP: Microcrystalline cellulose
   JP: Microcrystalline cellulose
   PhEur: Cellulosum microcristallinum
   USPNF: Microcrystalline cellulose
2. **Synonyms:**
   Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.
3. **Chemical Name :**
   Cellulose
4. **Empirical Formula and molecular weight :**
   $(C_6H_{10}O_5)_n$ approx. 36,000
   where n is approx 220.
5. **Structural Formula:**



6. **Functional Category:**
   Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.
7. **Applications in pharmaceutical formulation or technology:**
   binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes
8. **Description:**
   Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.
9. **Typical Properties :**
   Density (bulk) : 0.337 g/cm3
   Density (tapped): 0.478 g/cm3
   Density (true) : 1.512–1.668 g/cm3
   Melting range : chars at 260–270˚C.
   Solubility : slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

MAGESIUM STEARATE [40] :

1.Nonproprietary Names:

BP/JP/USPF : Magnesium stearate.
Ph Eur : Magnesii stearas.

2. Synonyms:

Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.

3. Chemical Name :

Octadecanoic acid magnesium salt.

4. Empirical Formula :

C36H70MgO4

5. Molecular weight :

591.34

6. **Structural Formula:**

$[CH_3(CH_2)_{16}COO]_2Mg$

7. Functional Category:

USP : Tablet and capsule lubricant.
BP/EP : lubricant, pharmaceutical aid.
Others : Glidant, anti-adherent.

8. Applications in pharmaceutical formulation or technology:

Tablet and capsule lubricant, glidant or anti-adherent.

9. **Description:**

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste.

10. Typical Properties :

Density (bulk) : 0.159 g/cm3
Density (tapped): 0.286 g/cm3
Density (true) : 1.092 g/cm3
Melting range : 117–1508C (commercial samples);
126–1308C (high purity magnesium stearate).
Solubility : Practically insoluble in ethanol, ether and water; slightly soluble in warm benzene and ethanol (95%).

TALC [40] :

1. **Nonproprietary Names**
   BP : Purified talc
   JP : Talc
   PhEur : Talcum
   USP : Talc
2. **Synonyms :**
   Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.
3. **Chemical Name :**
   Talc
4. **Empirical Formula :**
   Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$.
5. **Molecular Weight :**
   379.3 g/mol
6. **Functional Category :**
   Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant
7. **Applications in pharmaceutical formulation or technology :**
   Talc was once widely used in oral solid dosage formulations as a lubricant and diluent. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.
8. **Description :**
   Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.
9. **Typical properties :**
   Acidity/alkalinity: pH 7–10 for a 20% w/v aqueous dispersion.
   Solubility : Practically insoluble in dilute acids and alkalis, organic solvents, and water.

7. MATERIALS AND METHODS

Table No.1 List of materials and their applications in formulation

Name of the materials	Use in formulation
Metformin HCl	Active ingredient
Gliclazide	Active ingredient
HPMC $K_{100}M$	Hydrophilic polymer
Xanthan gum	Hydrophilic polymer
MCCP Ph 102	Directly compressible diluent
Iso propyl alcohol	Binder
Cross carmellose sodium	Super disintegrant
Cross povidone	Super disintegrant
Sodium starch glycolate	Super disintegrant
Magnesium stearate	Glidant
Talc	Lubricant

Table No:2 Equipments used for the Research Work

S.No	Insrtuments Used	Manufacturing company
1.	Digital Balance	Shimatzu LB 300
2.	Tablet hardness tester	Pfizer hardness tester
3.	Friability tester	Riche Pharma
4.	Vernier Caliper	Mitutoyo digimatic caliper
5.	Dissolution apparatus USP	Electrolab tablet dissolution apparatus
6.	Double beam UV Spectrophotometer	Shimatzu UV-1800
7.	Rotary tablet punching machine	Cadmach
8.	pH meter	Elico Ll120
9.	FT-IR Spectrophotometer	KBR press model M15

7.1. PREFORMULATION STUDIES:

Preformulation studies are the first step in the rational development of dosage form. It is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. Preformulation investigations are designed to identify those physicochemical properties of excipients that may influence the formulation design, method of manufacture and pharmacokinetic-biopharmaceutical properties of the resulting product. Following are the test performed for the preformulation study.

7.1.1. Melting point determination of Active ingredients:

Definite quantities of active ingredients were taken in different capillary tubes and their melting points were determined and matched with standards.

7.1.2. Determination of λ_{max}:

Metformin HCl:

Solution of metformin hydrochloride in water having a known concentration of about 10 µg/ml was prepared. Solution was then scanned in UV range of 200-400 nm using distilled water as a blank and wavelength of maximum absorption was found.

Gliclazide:

An accurately weighed 5 mg of Gliclazide was dissolved in 10 ml of methanol in a 50 ml volumetric flask and the volume was adjusted up to the mark with distilled water to obtain a stock solution of 100 µg/ml. The solution was filtered through Whatman filter paper No. 41. 0.2 ml of stock solution was transferred to 10 ml of volumetric flask and volume in flask was adjusted to 10 ml with distilled water to obtain a concentration of range of 2µg/ml. Solution was scanned in UV range of 200-400 nm using methanol: distilled water (1:4) as a blank and wavelength of maximum absorption was found.

7.1.3. Drug and Drug-Excipient physical compatibility studies:

The active ingredients and other excipients were mixed and taken in 2 ml glass vials and sealed. Then these glass vials were kept at room temperature and 40^0C/75%RH for about 1 month. The samples were withdrawn and analysed for colour change for every 10 days.

7.1.4. Chemical compatibility studies by FTIR:

IR spectra of drug and polymers and all super disintegrants alone and along with drug in KBr pellets at moderate scanning speed between 4000-400cm^{-1} was carried out using FTIR. The peak values and the possibility of functional groups shown in spectra were compared with standard values.

7.1.5. CALIBRATION CURVE:

For Metformin HCl:

An ultraviolet (UV) spectrophotometric method in water was used for estimation of Metformin HCl in water at 232nm. Absorbance was measured in the concentration range of 0-10 gm/ml.

For Gliclazide:

An accurately weighed 5 mg of Gliclazide was dissolved in 10 ml of methanol in a 50 ml volumetric flask and the volume was adjusted up to the mark with distilled water to obtain a stock solution of 100 µg/ml. The solution was filtered through Whatman filter paper No. 41. An appropriate aliquot portions of 0.2 to 1.0 ml of stock solution were transferred to a series of 10 ml volumetric flasks and volume in each flask were adjusted to 10 ml with distilled water to obtain a concentration of range of 2-10 µg/ml.

7.2. FORMULATION DEVELOPMENT:

Formulation of granules:

7.2.1. Formulation of sustained release matrix Metformin HCl granules:

Different batches of Metformin HCl sustained release layer (F_1 to F_6) were prepared with varying concentrations of different formulation ingredients according to Table no.2. Pass all the material in 80 mesh except MCCP Ph102 and it was in 60 mesh. Mix well Metformin HCl, polymer, MCCP pH 102 then add Iso propyl alcohol to the mixer, blend well to form a coherent mass and dried in an oven and pass the granules in 18 mesh. The granules were lubricated with Magnesium stearate and Talc. The amount required for the formulation given in the below Table no.2

Table No.3 Formulation of SR tablets (Wt in mg)

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6
Metformin HCl	500	500	500	500	500	500
$HPMCK_{100}M$	-	-	-	100	150	200
Xanthan gum	100	150	200	-	-	-
MCCP Ph102	140	90	40	140	90	40
Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s
Talc	5	5	5	5	5	5
Mg stearate	5	5	5	5	5	5
Total wt	750	750	750	750	750	750

Table No.4 Polymer concentration used with respect to drug Metformin HCl

Polymers	F_1	F_2	F_3	F_4	F_5	F_6
$HPMCK_{100}M$	-	-	-	20	30	40
Xanthan gum	20	30	40	-	-	-

7.2.2. Formulation of immediate release Gliclazide layer:

An immediate release Gliclazide layer was prepared by direct compression according to Table no.4. Pass Gliclazide, talc, Mg stearate in 100 mesh and MCCP pH 102, Crospovidone, Cross carmellose sodium, SSG in 60 mesh. Mix the ingredient well. The amount required for formulation given in Table no.4.

Table No.5 Formulation of IR tablets (Wt in mg)

Ingredients	IR_1	IR_2	IR_3
Gliclazide	40	40	40
MCCP pH102	12	12	12
Croscarmellose sodium	7	-	-
SSG	-	7	-
Crospovidone	-	-	7
Indigo blue	q.s	q.s	q.s
Mg stearate	0.5	0.5	0.5
Talc	0.5	0.5	0.5
Total Weight of 1 tablet	60	60	60

Formulation of tablets:

a) **Formulation of sustained release tablets :**

The sustained release tablet was compressed in 13mm diameter with flat biconvex tablet.

b) **Formulation of immediate release tablets :**

The immediate release tablet was compressed in 5.5mm diameter with flat biconvex tablet.

7.3. PRE COMPRESSION STUDIES ON GRANULES:

7.3.1. Bulk Density (Db):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M / Vb$$

Where, M is the mass of powder

Vb is the bulk volume of the powder.

7.3.2. Tapped Density (Dt):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$\mathbf{Dt = M / Vt}$$

Where, M is the mass of powder

Vt is the tapped volume of the powder.

7.3.3. Angle of Repose (θ):

The friction forces in a loose powder can be measured by the angle of repose (θ). It is an indicative of the flow properties of the powder.

It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\mathbf{\tan(\theta) = h / r}$$

$$\mathbf{\theta = \tan^{-1}(h / r)}$$

Where, is the angle of repose.

h is the height in cms

r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property is shown in Table no.5.

Table No.6 : Angle of Repose as an Indication of Powder Flow Properties

S.No.	angle of repose	Type of flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Very poor

7.3.4. Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is given as

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where, Dt is the tapped density of the powder and

Db is the bulk density of the powder.

Table No.7: Relationship between % compressibility and flow ability

% compressibility	Flow ability
5-12	Excellent
12-16	Good
18-21	Fair passable
23-35	Poor
33-38	Very poor
>40	Very very poor

7.3.5. Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{Dt}{Db}$$

Where, Dt is the tapped density

Db is the bulk density.

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

7.4. POST COMPRESSION STUDIES OF TABLETS:

7.4.1. Description:

The general appearance of a tablet like size, shape, colour, coated or uncoated should be observed. It is needed for consumer acceptance and during storage physical changes may happen which can be easily matched with description.

7.4.2. Weight variation:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in table no.7.

Table No.8: Weight Variation Specification as per IP

Average weight of tablet	% deviation
80 mg or less	±10
More than 80 mg but less than 250mg	±7.5
250 mg or more	±5

7.4.3. Thickness:

It can be dimensionally described and controlled. Thickness may affect the hardness, disintegration time and dissolution rate. Tablet thickness can be measured by vernier callipers for six tablets.

7.4.4. Hardness:

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm2.

7.4.5. Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighed sample of 6 tablets were placed in the friabilator and were subjected to the 100 revolutions for 4 min. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

7.4.6. Tablet disintegration time:

Tablet disintegration study was performed only for immediate release tablet and for the immediate release layer of inlay tablet. Disintegration time was determined using USP tablet disintegration tester in distilled water.

7.4.7. Assay:

For sustained release tablets:

Standard preparation: Prepare a solution of metformin hydrochloride in water having a known concentration of about 10 µg/ml.

Weigh and finely powder 20 tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of metformin hydrochloride, to 100ml volumetric flask. Add 70ml of water shake by mechanical means for 15 minutes, dilute with water to volume,

and filter, discarding the first 20ml of the filtrate. Dilute 10ml of the filtrate with water to 100ml, and dilute 10ml of the resulting solution with water to 100ml.

For immediate release tablets:

Crush one tab on butter paper and transfer an accurately an accurately weighed Gliclazide, without loss to 500ml volumetric flask, add 20ml methanol sonicate for 5min add 200ml of diluent and shake mechanically for 60min make vol up to mark with diluent. Filter solution to 20ml volumetric flask and dilute up to mark with diluent. Take the absorbance at 226 nm using diluent as a blank for a background correction. Take absorbance in triplicate of a standard solution and duplicate of a sample preparation.

7.4.8. In vitro dissolution studies:

Dissolution study of sustained release and immediate release of different tablet formulations were carried out separately.

Dissolution of sustained release tablet:

Apparatus: USP Type II (Paddle type)

Medium : 6.8 pH phosphate buffer

Rpm : 100

Volume : 900ml

Temp : 37.5°C

The study was carried out for 12 hours. 10ml of samples were withdrawn on time interval of 1, 3, 6, 9, 12^{th} hour and replaced with fresh medium. Samples were filtered, diluted and absorbance was measured at 232 nm using UV- VIS Spectrophotometer.

Standard preparation: Prepare a solution of metformin hydrochloride in water having a known concentration of about 10 µg/ml.

The percentage of metformin HCl release was calculated. The limit for extended release tablet for 12 hours as follows.

Table No.9: Limits for SR formulation release

Time in hours	500mg tablet, amount dissolved
1	Between 20% and 40%
3	Between 45% and 65%
10	Not less than 85%

Dissolution of immediate release tablet:

Dissolution studies were carried out by USP paddle method Type II apparatus at 37± 0.50° C, taking 900ml of phosphate buffer pH 6.8 as a dissolution medium. Speed of rotation of paddle was set at 50rpm. Absorbance of sample was measured at 226 nm by using UV spectrophotometer.

7.4.9. For inlay tablet:

7.4.9.1. Swelling and erosion studies:

The rate of test medium uptake by the pectin polymer was determined by equilibrium weight gain method. The inlay tablets were accurately weighed (W_0), placed in the basket of dissolution apparatus, rotating at 100rpm, 37±0.5°C temperature, using pH 6.8 phosphate buffer. After 1, 2, 3, 5, 7, 9 and 12 hours, each basket was removed from the dissolution apparatus, the tablet with the pre-weighed mesh was withdrawn from the medium and lightly bottled with tissue paper to remove excess test liquid and then reweighed (W_1). After the swelling studies, the wet samples were then dried in an oven at 80°C for 12 hour time period, allowed cooling in desiccators and finally weighed until constant weight was achieved (final dry weight, W_2). The experiment was performed for 6 times for each time point and fresh samples were used for each individual time point. The percentage increase in weight due to absorbed liquid or water uptake was estimated at each time point from the following equation

Swelling % = W_1-W_0/W_0×100,

Erosion % = W_0-W_2/W_0×100

7.4.9.2. Assay of inlay tablet:

Assay of inlay tablet containing metformin HCl and gliclazide done by two steps. The assay of inlay tablet SR layer containing metformin HCl was analyzed by UV method as directed in the assay as of SR tablet. The assay of inlay tablet IR layer containing gliclazide was analyzed by UV method as directed in the assay as of IR tablet.

7.4.9.3. In vitro dissolution profile of inlay tablet:

Dissolution medium is separately chosen for both the drugs based on their individual solubility and their absorption site in the GIT.

Separate dissolution conditions were decided, one for each API.

1. The dissolution of sustained release layer was studied with dissolution medium of 6.8 pH phosphate buffer for 12 hours as directed in assay of SR tablet.
2. The dissolution of immediate release layer was studied with dissolution medium of 6.8 pH phosphate buffer for 30 minutes.

7.4.9.4. Evaluation of invitro release kinetics:

To study kinetics, data obtained from in vitro release were plotted in various kinetic models.

1. **Zero order equation:**

   If the release rate follows zero order then, the slope can be obtained by plotting % drug :released Vs time in hours. It is an ideal release profile to achieve pharmacological prolonged action. The release rate was independent of concentration.

   $$\mathbf{C=K_0t}$$

   Where K_0 – zero order constant in conc/time

   t-time in hours

2. **First order equation:**

   The graph was plotted as log % cumulative drug remaining vs time in hours

   $$\mathbf{\log C=\log C_0-Kt/2.303}$$

   where C_0- initial concentration of drug

   K- first order constant and t-time

3. **Higuchi kinetics:**

The graph was plotted as % cummulative drug release vs time in hours

$$Q = Kt^{1/2}$$

Where K-constant reflecting design variable system

t-time in hours

Hence drug release rate is proportional to the reciprocal of square root of time. If the plot yields a straight line, and the slope is one, then the particular dosage form is considered to follow higuchi kinetics of drug release.

4. **Hixson and crowell erosion equation:**

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and cowell rate equation. The graph was plotted by cube root of % drug remaining Vs time in hours.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}t$$

Where Q_t - amount of drug released in time t

Q_0 - initial amount of drug

K_{HC} - rate constant for Hixson crowell equation

5. **Korsmeyer – peppas equation:**

To evaluate mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released Vs time

$$M_t/M\infty = Kt^n$$

Where $M_t/M\infty$ - friction of drug released at time t

t – release time

K – kinetic constant

N – diffusional exponent indicative of the mechanism drug release

The n value could be obtained from slope of the plot of log cumulative % of drug released Vs log time. The results were tabulated.

Table No.10 Description of diffusion mechanism

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n >0.89	Super case-II transport

i. Zero Order Reaction - % Cumulative drug release Vs Time in hrs
ii. First Order Reaction – Log % Cumulative drug remaining Vs Time in hrs
iii. Higuchi kinetics - % Cumulative drug release Vs square root of time
iv. Korsmeyer – Peppas equation- log cumulative % of drug released Vs log time
v. Hixon and Crowell erosion equation – cube root of % drug remaining Vs time in hrs

7.4.10. Stability study:

Stability study of optimized inlay tablet was carried out at room temperature and at an accelerated condition of 40^0/75 RH for a period of 3 months. Samples were withdrawn at an interval of 1 month for evaluation with respect to physical parameters, assay and dissolution studies.

8. RESULTS AND DISCUSSION

8.1. PREFORMULATION STUDIES:

The overall objective of preformulation studies is to generate useful information to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

8.1.1. Melting point determination of Active ingredients:

Melting point of active ingredients was determined by capillary method. The result was shown in table below.

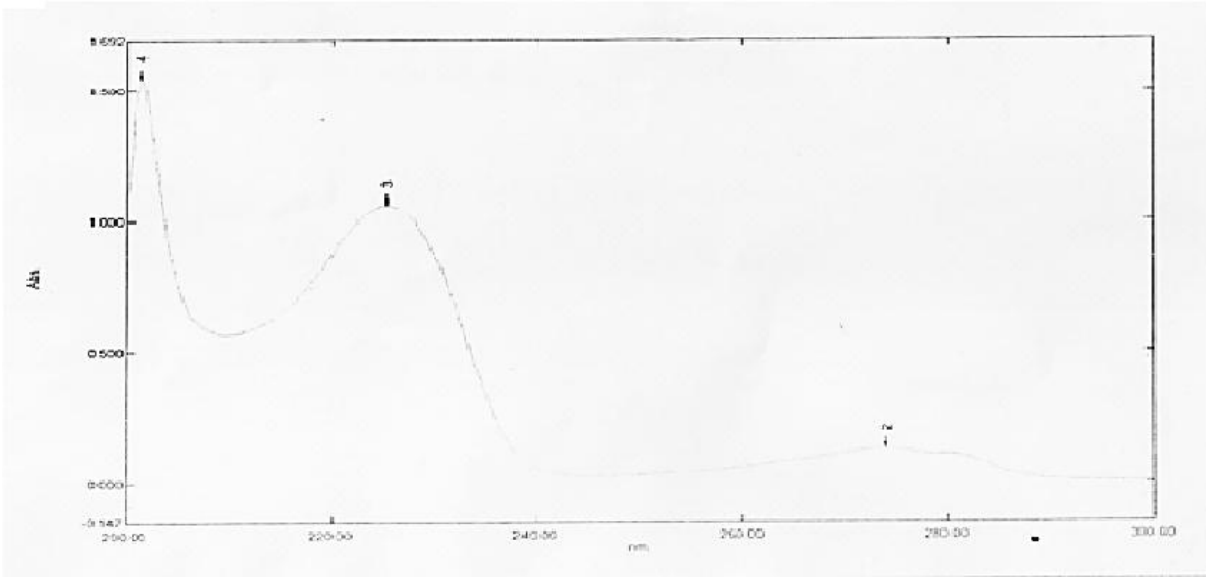
Drug	Specification	Observation
Metformin hydrochloride	222-226^{0}C	224.74±0.048^{0}C
Gliclazide	181^{0}C	180±0.83^{0}C

8.1.2. Determination of λ_{max}:

For Metformin HCl :

Metformin HCl drug solution in water was scanned using UV-Spectrophotometer between the range 210-400nm using water as blank and the maximum absorbance (λ max) was found at 232nm.

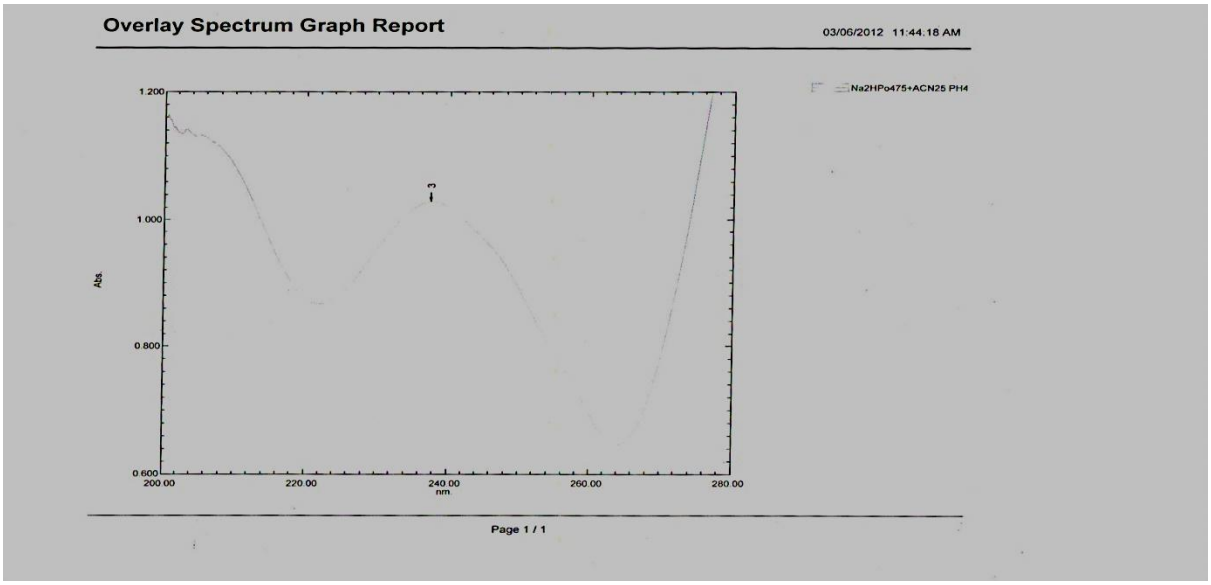
Fig No.4. Spectrum of Metformin HCl



For Gliclazide :

Gliclazide drug solution was scanned using UV-Spectrophotometer between the range 210-400nm using methanol:distilled water as blank and the maximum absorbance (λ max) was found at 229.5nm.

Fig No.5 Spectrum of Gliclazide



8.1.3. Drug-excipient physical compatibility studies:

The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients that are added in the formulation. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious and easy and safe to administer.

The physical compatibility evaluation was performed in visual basis. The study implies that the drug, polymer and other excipients were physically compatible with each other as there were no changes of physically. The results have been shown in the table no.11.

8.1.4. Chemical compatibility studies by FTIR:

The IR spectral analysis of Metformin hydrochloride, Gliclazide, polymers and other excipients was shown from fig no.6 to fig no.18. All the characteristic peaks appear for the pure Metformin HCl, Gliclazide and its physical mixture indicating no interaction between the two drugs. Both drugs with polymers also show characteristic peaks so, no interaction between the drugs and excipients.

Table No.11: Drug – Excipients Physical compatibility studies.

S.No	Drug+Excipients	Description at initial day	RT,40^{0}C/75%RH In days		
			10th	20th	30th
1.	MH	White, Crystalline powder	NC	NC	NC
2.	GL	White, Crystalline powder	NC	NC	NC
3.	MH+GL	White, Crystalline powder	NC	NC	NC
4.	XG	Creamy yellow crystalline powder	NC	NC	NC
5.	HPMC $K_{100}M$	White, creamy crystalline powder	NC	NC	NC
6.	SSG	White, free-flowing hygroscopic powder	NC	NC	NC
7.	CP	White, crystalline powder	NC	NC	NC
8.	CCS	White or greyish white powder	NC	NC	NC
9.	MCC pH102	White, crystalline powder	NC	NC	NC
10.	Mg.S	White, crystalline powder	NC	NC	NC
11.	Talc	White or greyish white powder	NC	NC	NC
12.	MH+GL+XG	White, crystalline powder	NC	NC	NC
13.	MH+GL+HPMC	White, crystalline powder	NC	NC	NC
14.	MH+GL+SSG	White, crystalline powder	NC	NC	NC
15.	MH+GL+CP	White, crystalline powder	NC	NC	NC
16.	MH+GL+CCS	White, crystalline powder	NC	NC	NC
17.	MH+GL+All	White, crystalline powder	NC	NC	NC

MH-Metformin HCl, **GL**-Gliclazide, **XG**-Xantan gum, **HPMC $K_{100}M$**-Hydroxy propyl methyl cellulose Grade, **SSG**-Sodium starch glycolate, **CP**-Cross povidone, **CCS**-Croscarmellose sodium, **MCC pH102**-Microcrystalline cellulose grade, **NC**-No Change

Chemical compatibility studies by FT-IR:

Fig No.6 Metformin HCl

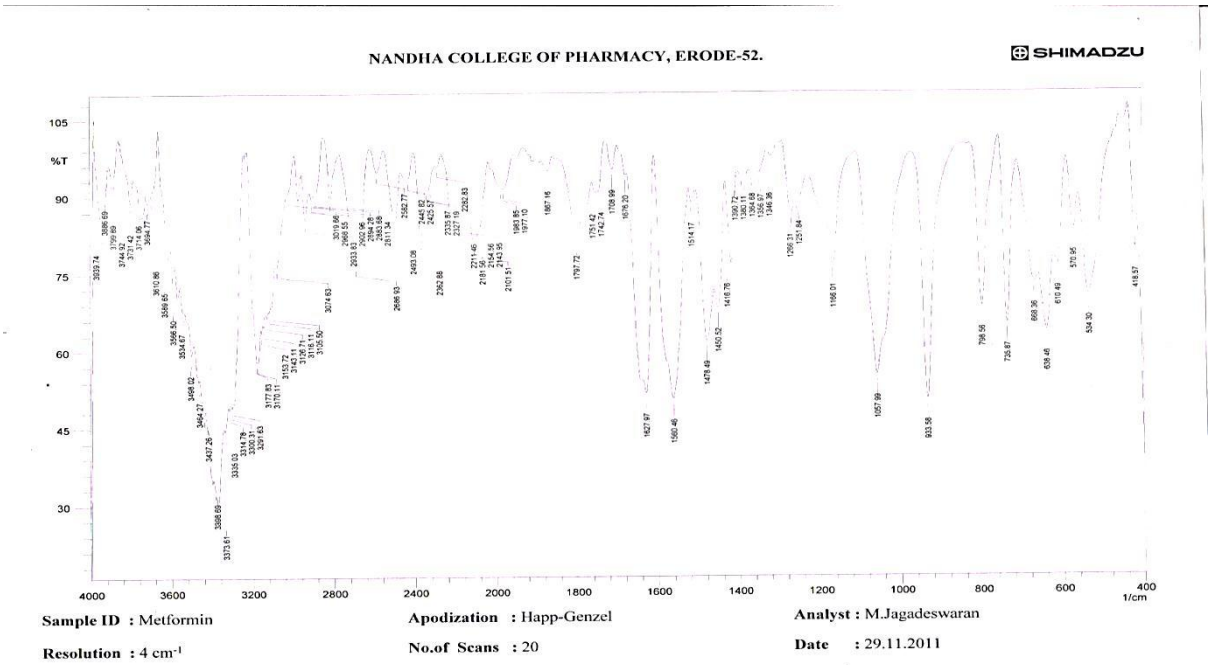


Fig No.7 Gliclazide

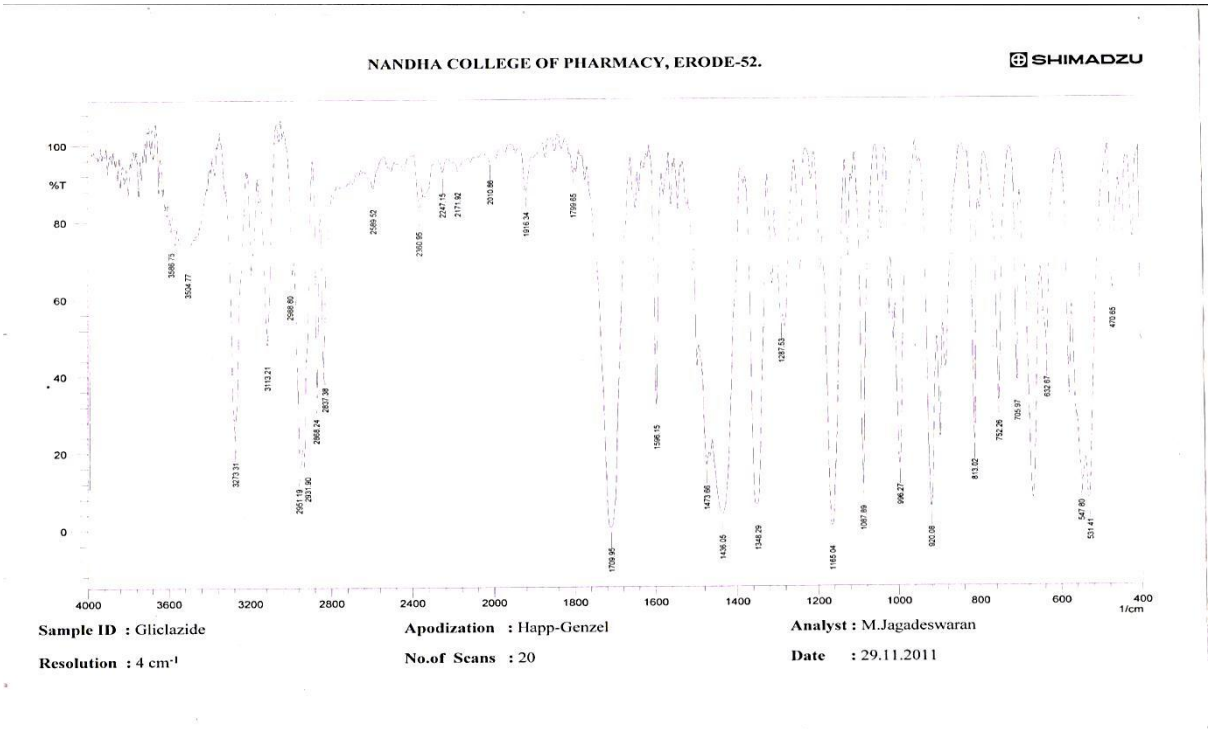


Fig No.8 Metformin HCl + Gliclazide

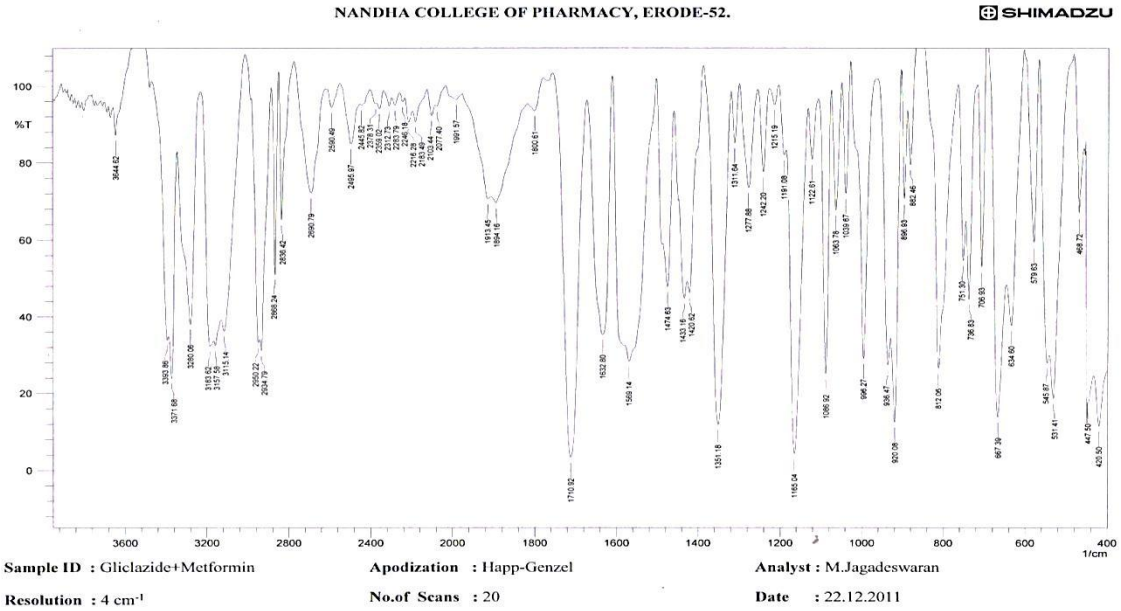


Fig No.9 HPMC

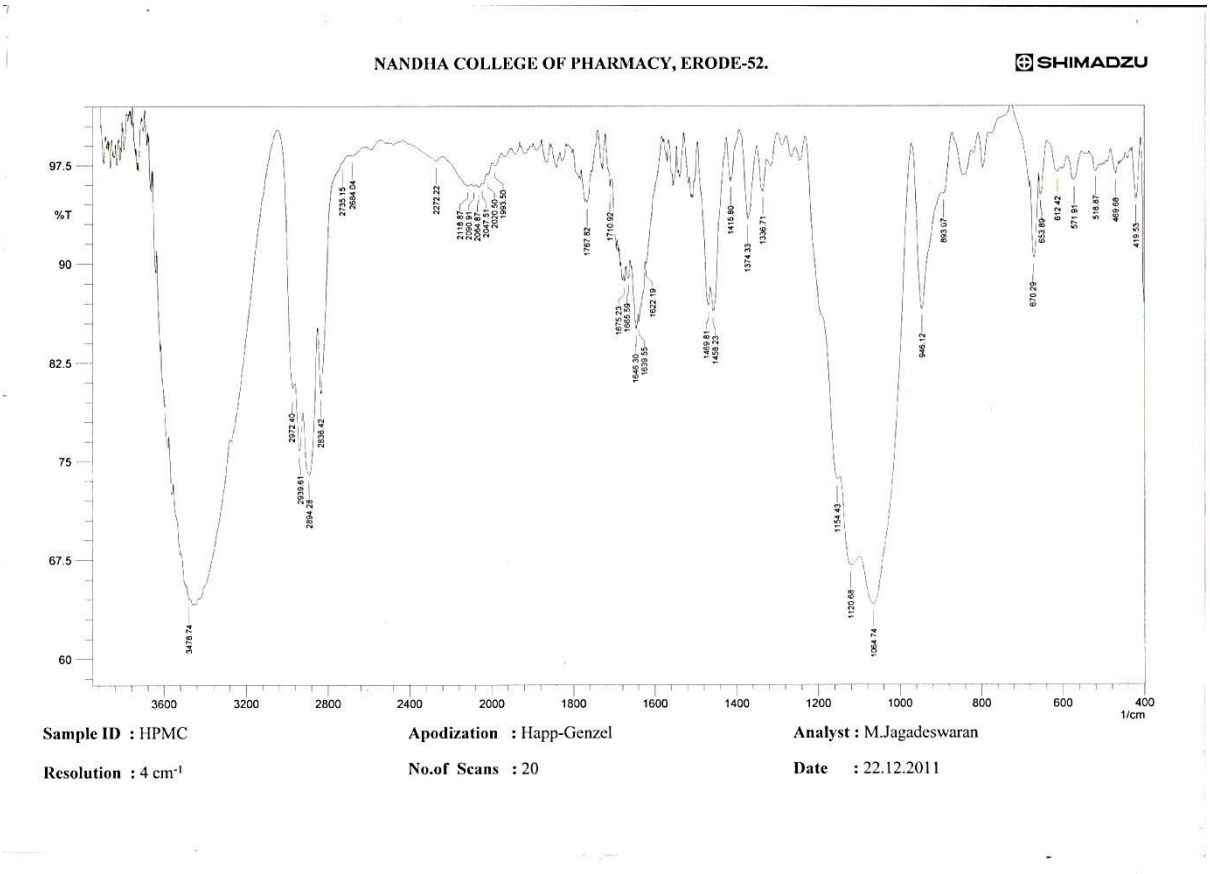


Fig No.10 Xanthan gum

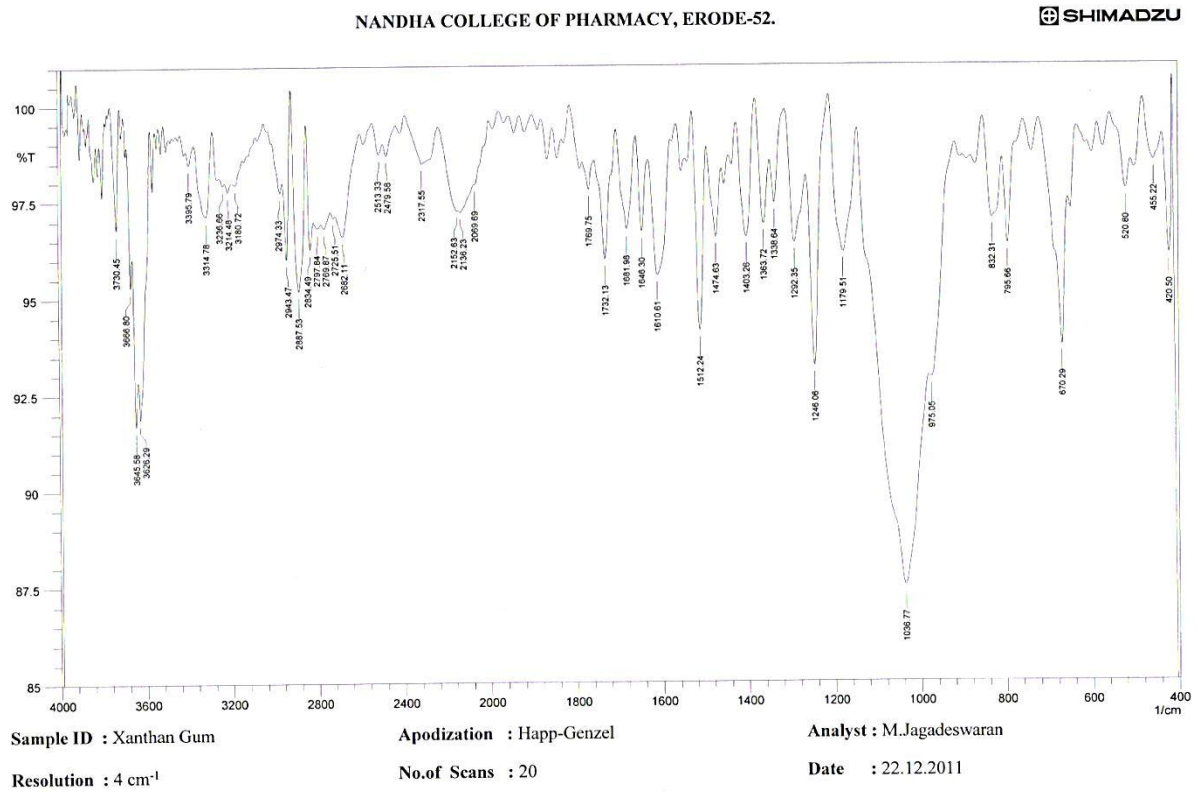


Fig No.11 Sodium starch glycolate

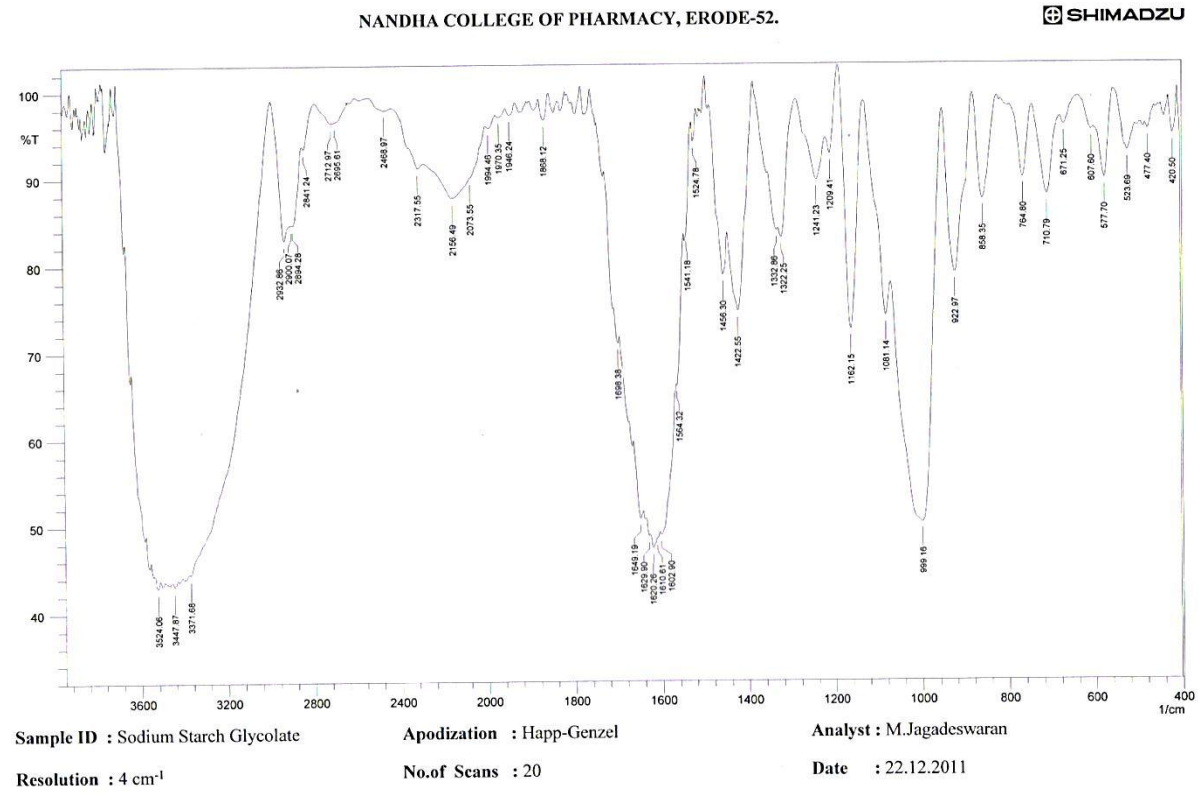


Fig No.12 Croscarmellose sodium

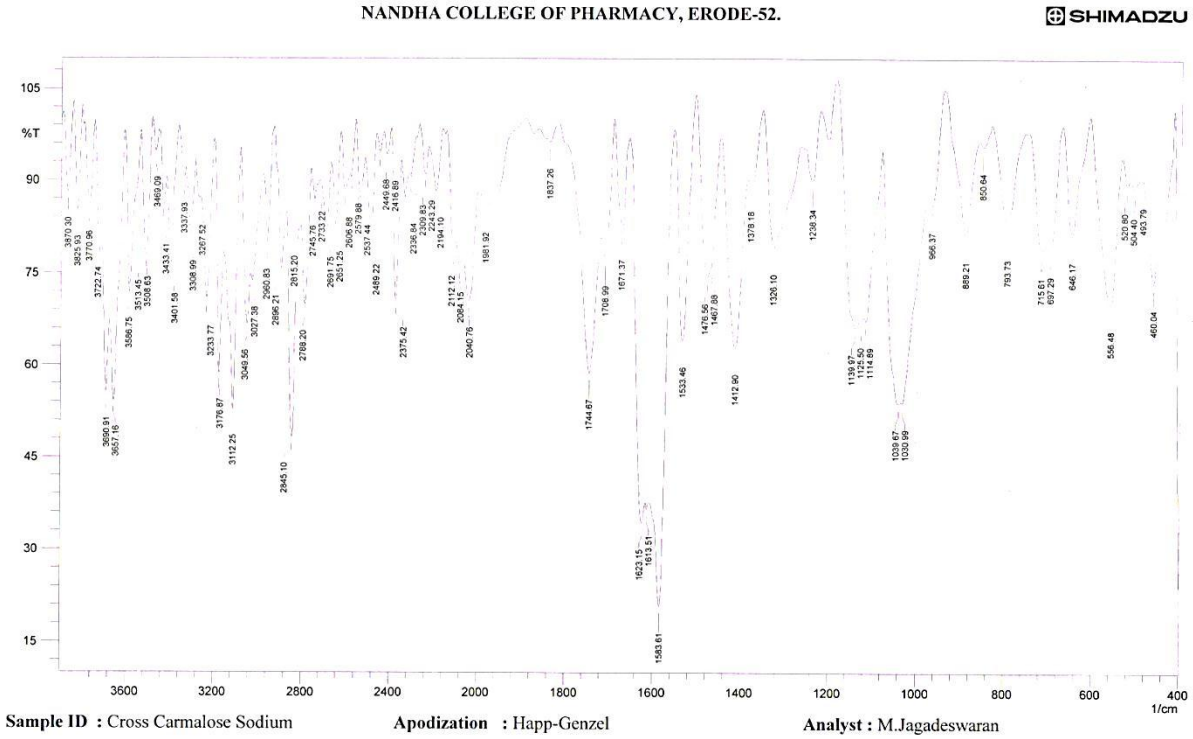


Fig No.13 Crospovidone

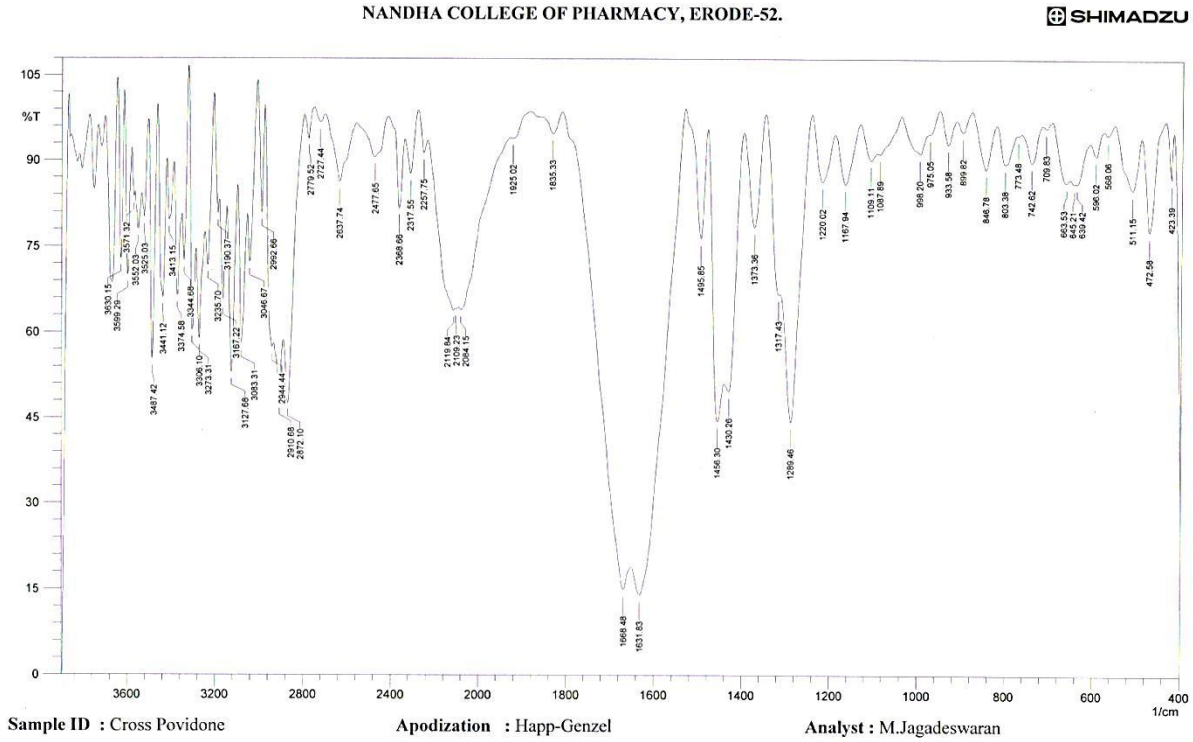


Fig No.14 Metformin HCl + HPMC

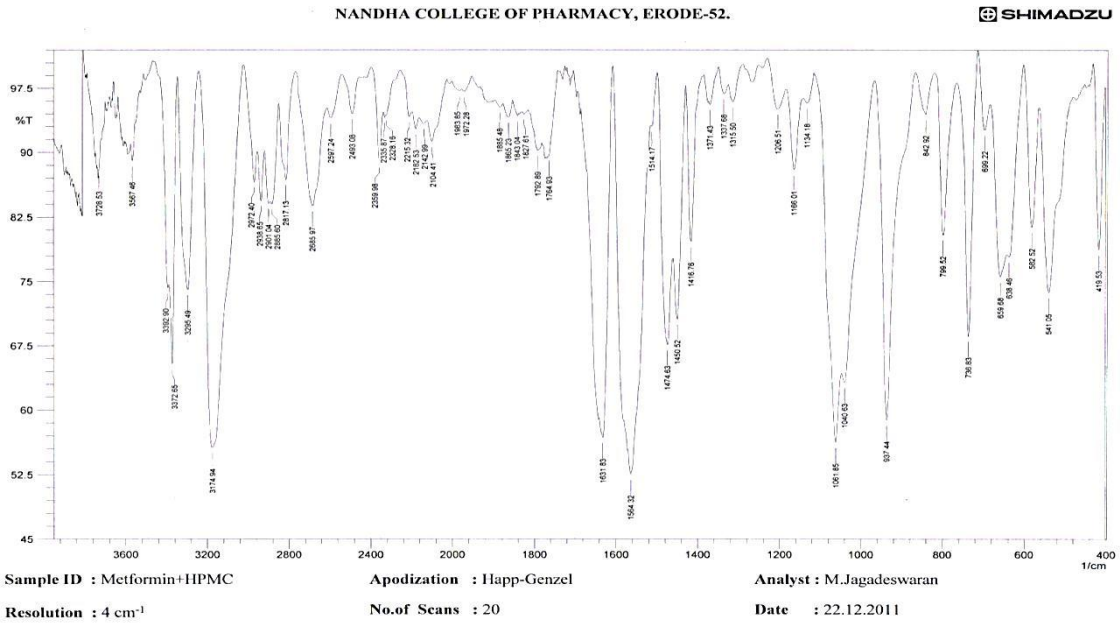


Fig No.15 Metformin HCl + Xanthan gum

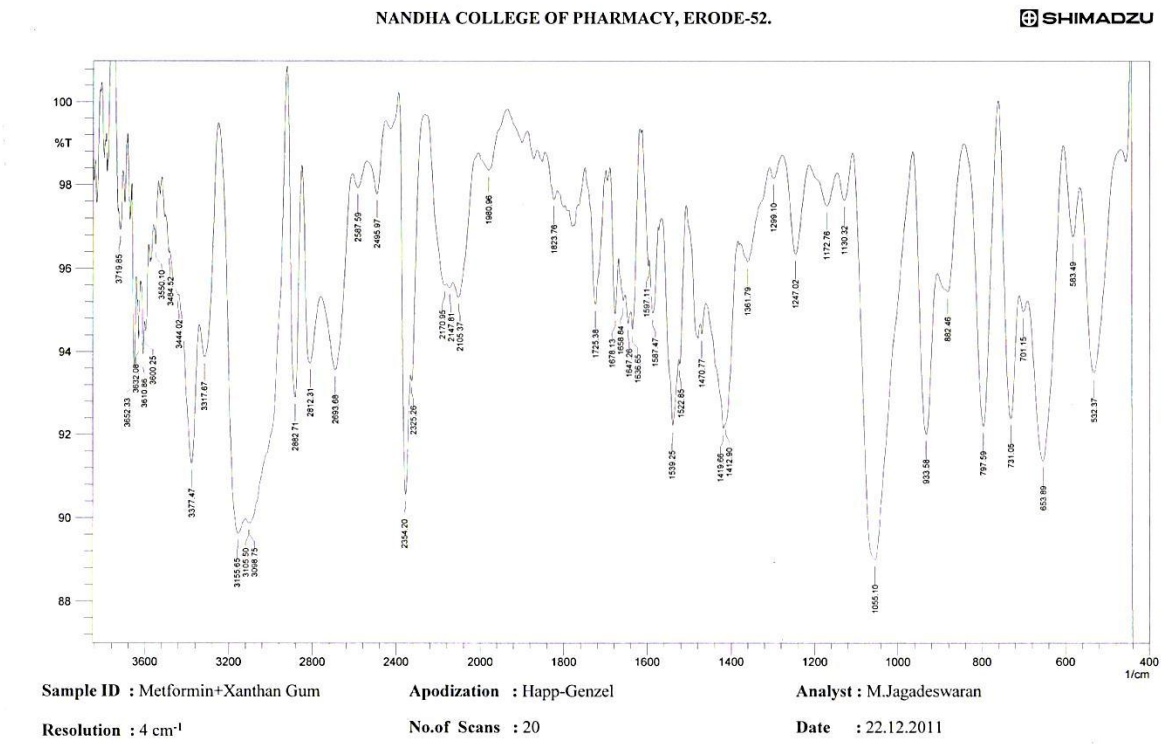


Fig No.16 Gliclazide + Sodium starch glycolate

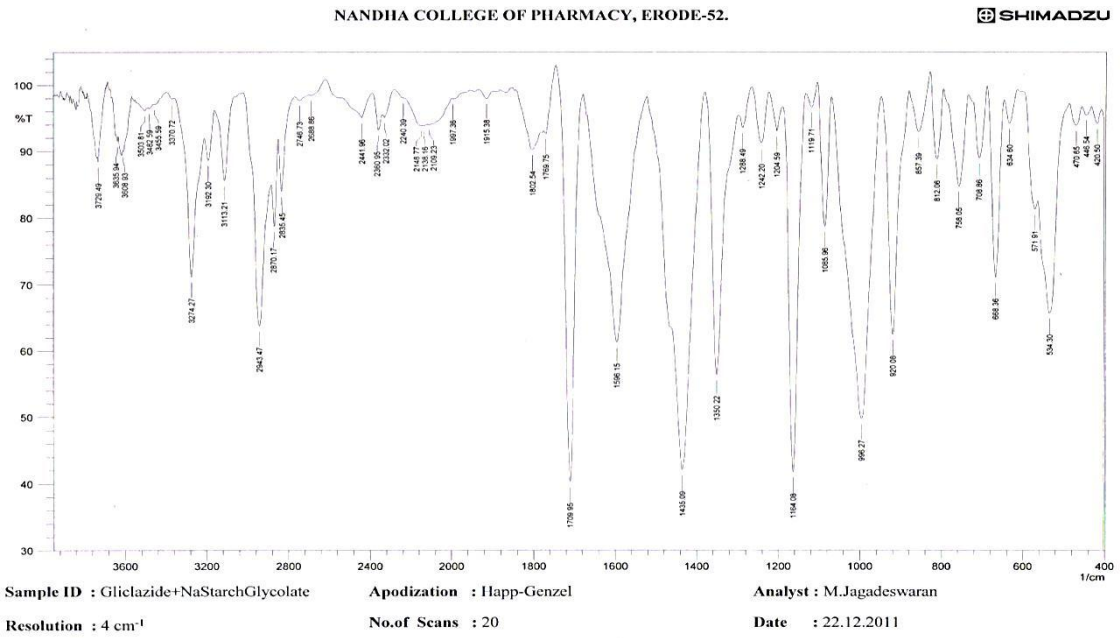


Fig No.17 Gliclazide + Croscarmellose sodium

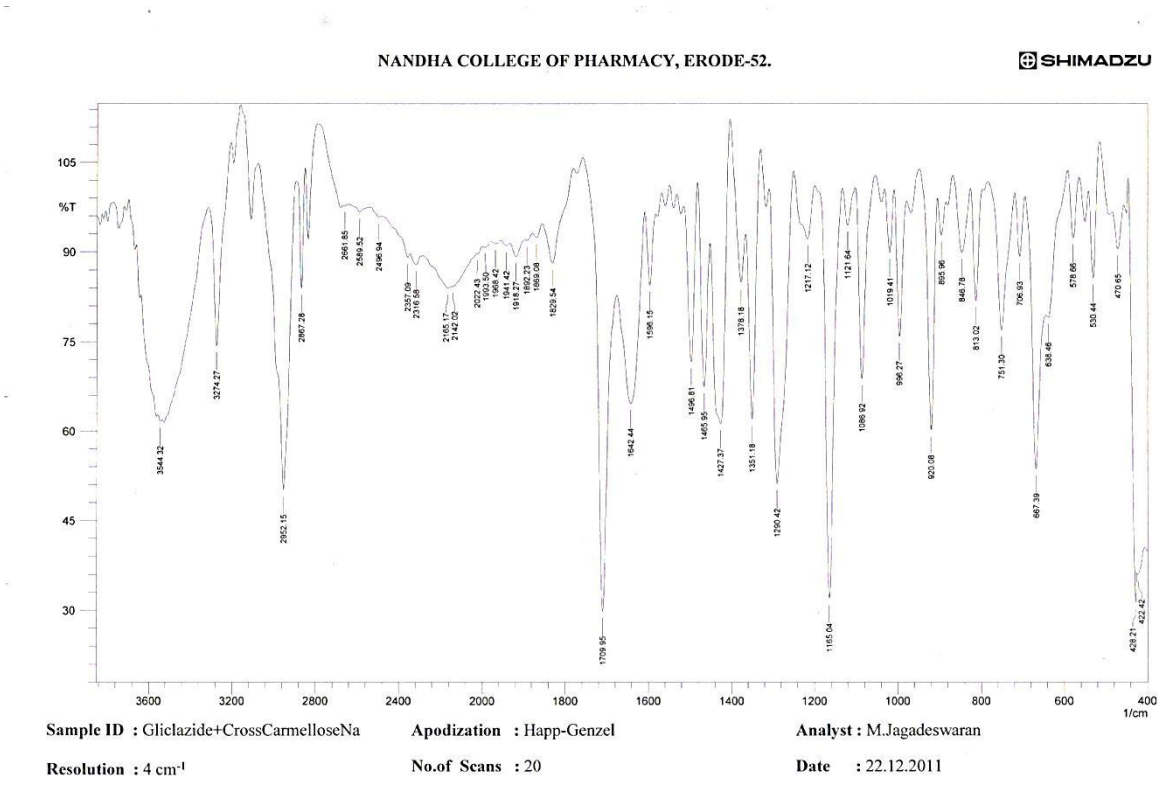
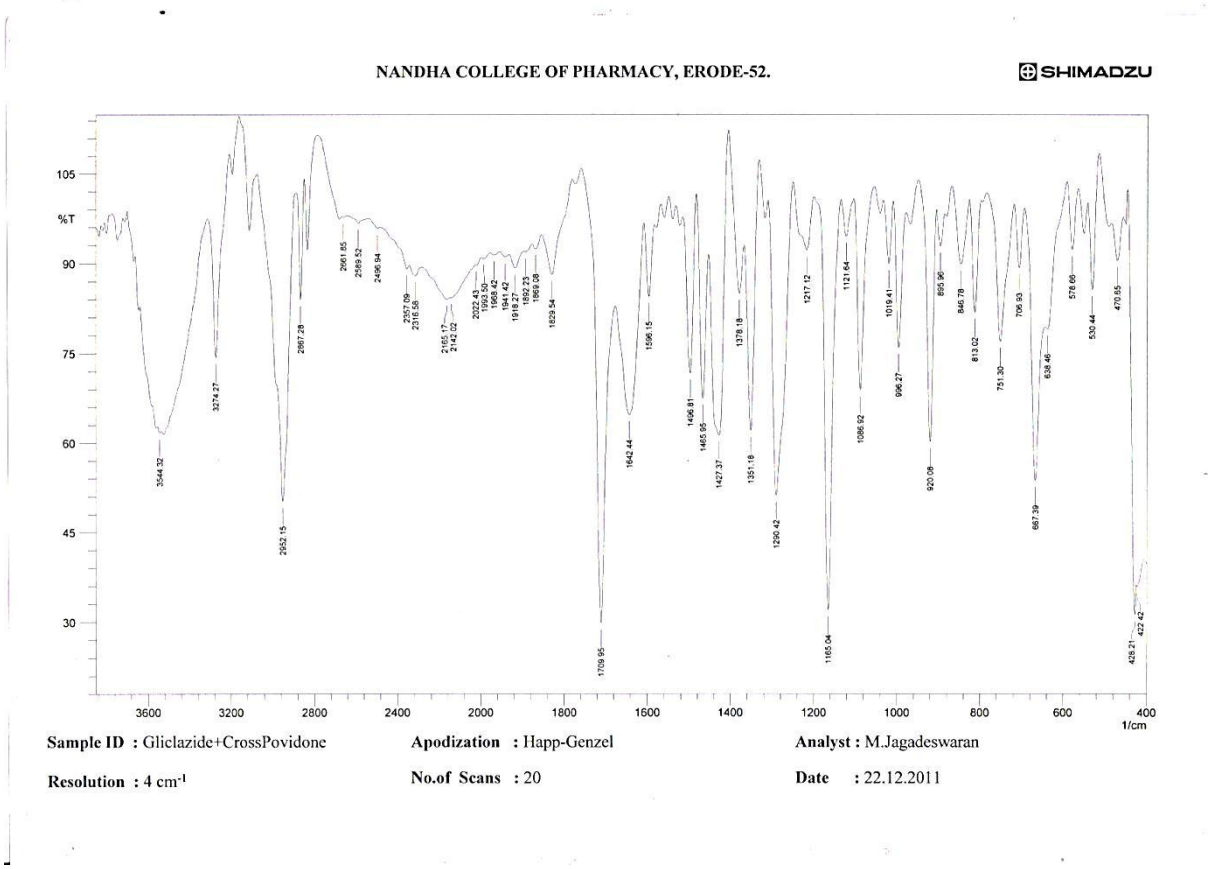


Fig No.18 Gliclazide + Crospovidone



8.1.5. CALIBRATION CURVE:

a) Metformin hydrochloride:

The absorbance of solution of metformin hydrochloride in distilled water was observed at 232nm. It was found that the solutions show linearity (R^2 value 0.9998) in absorbance at a concentration of 0-10 µg/ml and obey beer lamberts law. The values shown in table no.12 and fig no.19.

b) Gliclazide:

An accurately weighed 5 mg of gliclazide was dissolved in 10 ml of methanol in a 50 ml volumetric flask and the volume was adjusted up to the mark with distilled water to obtain a stock solution of 100 µg/ml. The solution was filtered through Whatman filter paper No. 41. An appropriate aliquot portions of 0.2 to 1.0 ml of stock solution were transferred to a series of 10 ml volumetric flasks and volume in each flask were adjusted to 10 ml with distilled water to obtain a concentration of range of 2-10 µg/ml.

Table No.12: Calibration curve of Active ingredients

Metformin hydrochloride		Gliclazide	
Concentration (µg/ml)	**Absorbance**	**Concentration (µg/ml)**	**Absorbance**
0	0	0	0
2	0.281	2	0.159
4	0.573	4	0.316
6	0.838	6	0.443
8	1.119	8	0.611
10	1.387	10	0.775

Fig No.19 Calibration curve of Metformin HCl

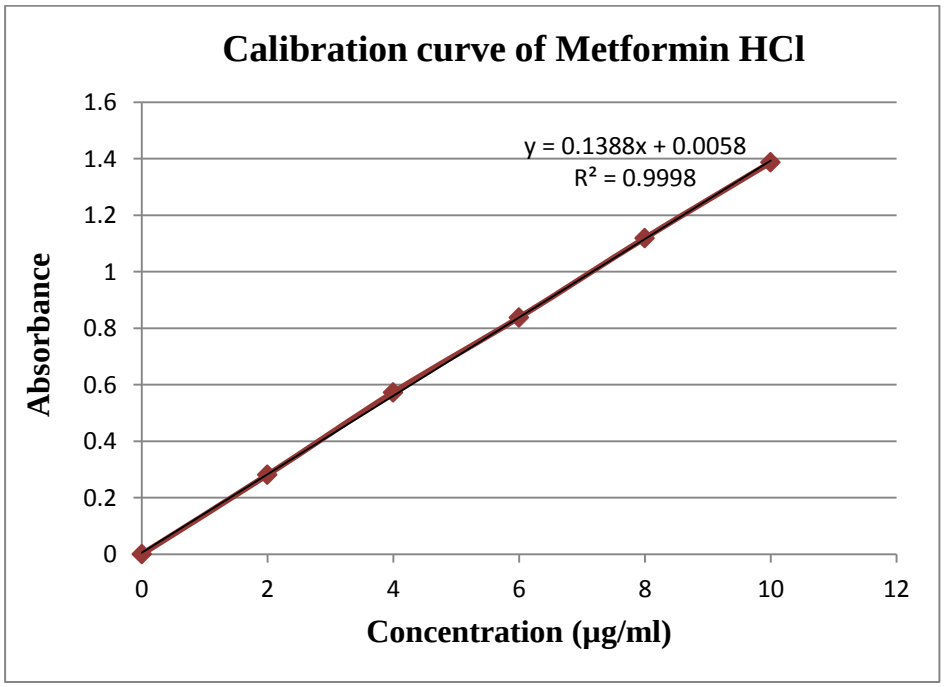
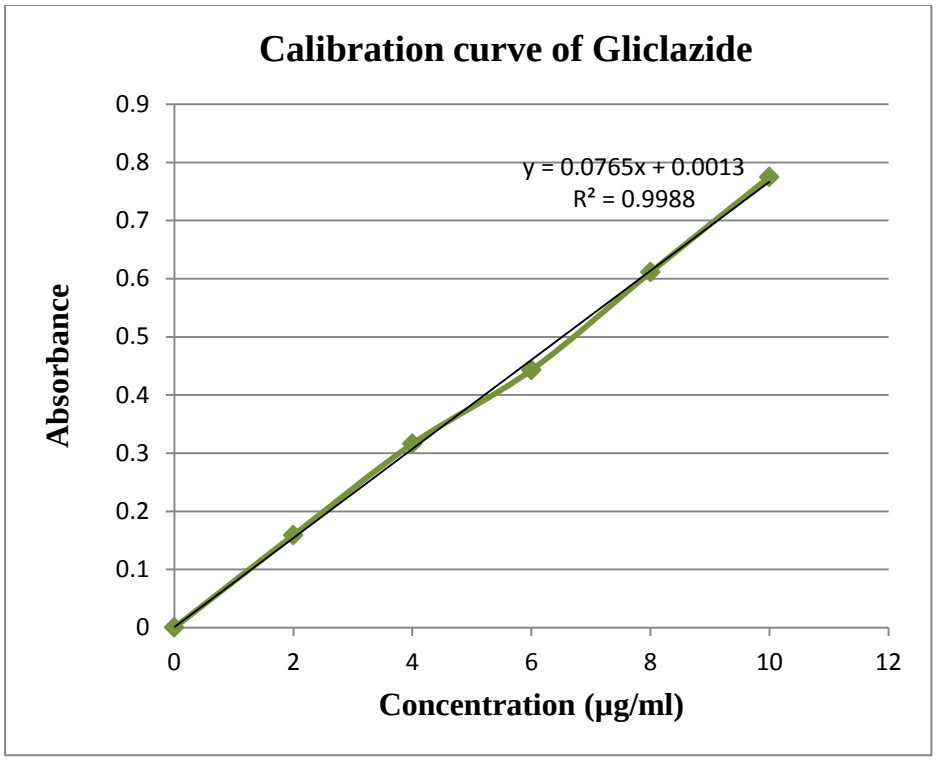


Fig No.20 Calibration curve of Gliclazide



8.2. PRECOMPRESSION STUDY SR FORMULATION:

8.2.1. Bulk density:

The bulk density of various granules prepared with different polymer was measured by graduated cylinder. The bulk density was found in the range from 0.499 to 0.522 g/cm^3. The results are presented in Table No.13.

8.2.2. Tapped density:

The tapped density of various granules prepared with different polymer was measured by measuring cylinder. The tapped density was found in the range from 0.583 to 0.606 g/cm^3. The results are given in Table No.13.

8.2.3. Compressibility index:

A flow property plays an important role in pharmaceuticals especially in tablet formulation because improper flow may cause more weight variation. Values of Carr's Index (Compressibility) below 15% usually give rise to good flow properties but readings above 25% indicate poor flow properties. The compressibility index of various granules prepared with different polymer using bulk density and tapped density data was calculated. It was

found in the range 13.5 to 14.5% and hence they exhibit good flow property. The results are given in Table No.13.

8.2.4. Hausner's ratio:

Hausner ratio is an indirect index of ease of powder flow. Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25). The hausner ratio of various granules prepared with different polymer was calculated by using bulk density and tapped density data. It was found in the range of 1.14 to 1.17 which indicates better flow property. The results are given in Table No.13.

8.2.5. Angle of repose (θ):

The angle of repose of various granules prepared with different polymer was measured by funnel method. Angle of repose was found in the ranges from 24.80^0 to 26.60^0. So, also evidenced with angle of repose that granules have a good flow property. The results are given in Table No.13.

Table No.13: Pre compression study SR formulation

Formulation	Bulk density* g/cm^3	Tapped density* g/cm^3	Compressibility index* g/cm^3	Hausner's ratio*	Angle of repose*
F_1	0.516±0.002	0.597±0.013	13.5±0.001	1.15±0.001	25.39±0.681
F_2	0.522±0.004	0.606±0.034	14.0±0.029	1.15±0.009	26.20±0.292
F_3	0.507±0.031	0.590±0.019	14.5±0.053	1.17±0.040	25.88±0.433
F_4	0.499±0.020	0.583±0.051	14.4±0.003	1.16±0.051	24.80±0.111
F_5	0.500±0.014	0.592±0.022	14.3±0.039	1.14±0.028	25.64±0.395
F_6	0.517±0.008	0.576±0.011	14.1±0.011	1.16±0.021	26.60±0.105

* Mean ± SD (n=3)

8.3. POST COMPRESSION STUDIES OF SR TABLETS:

8.3.1. Weight variation:

The theoretical average weight of the various formulated tablets are 750mg and weight variation of various formulation are depicted in Table No.14. The percentage deviation of the weight was within 5% as per monograph.

8.3.2. Hardness:

The hardness of various tablet formulation was shown in Table No.14. The hardness of the tablet was found in the ranges from 6.4 to 6.6 Kg/cm^2. So, it was the sufficient hardness for tablet coating, transporting and packing.

Table No.14: Post compression parameters of SR formulations

Formulation	Weight variation*	Hardness* (Kg/cm^2)	Thickness* (mm)	Friability* (%)	Drug content*(%)
F_1	750±4.15	6.5±0.255	6.48±0.113	0.38±0.102	98.30±0.05
F_2	750.4±6.1	6.4±0.491	6.42±0.017	0.49±0.026	98.03±0.06
F_3	749.7±5.83	6.6±0.204	6.61±0.129	0.58±0.034	98.13±0.01
F_4	749.6±7.97	6.4±0.258	6.63±0.092	0.69±0.045	98.33±0.04
F_5	751.1±4.21	6.5±0.273	6.62±0.089	0.30±0.019	99.56±0.03
F_6	749.2±5.82	6.6±0.418	6.52±0.214	0.69±0.040	99.80±0.02

*Mean ± SD (n=3)

8.3.3. Thickness:

The thickness of the various tablet formulation was shown in Table No.14. The thickness of the tablet was found in the ranges from 6.42 to 6.63 mm. It was important for packing of tablet and acceptance.

8.3.4. Friability:

The friability of the various tablet formulation was shown in table no.14. The friability of the tablet was found in the ranges from 0.30 to 0.69%. The values are within limit of the official monograph i.e., not more than 1%.

8.3.5. Drug content:

The content of the various formulations was analyzed by UV spectrometric method. It was very important for the release percentage from the amount present in the tablet. The percentage of drug found in the tablet ranges from 98.03 to 99.80% and was within the limits. The drug content of various formulations was shown in table no.14.

8.3.6. In Vitro Dissolution study of SR tablet:

Table No.15: In vitro dissolution profile SR tablet*

Formulation	Time in hrs				
	1	3	6	9	12
F_1	69.83±0.399	83.59±0.805	95.32±0.887	97.97±0.510	99.25±0.715
F_2	63.45±0.947	79.98±0.572	93.27±0.718	96.32±0.542	98.16±0.622
F_3	57.64±0.781	74.77±0.526	84.57±0.341	94.13±0.778	98.59±0.722
F_4	64.52±0.862	75.81±0.940	89.98±0.557	96.75±0.989	99.93±0.680
F_5	52.19±0.685	72.93±0.557	84.75±0.663	93.26±0.560	99.14±0.887
F_6	30.72±0.546	51.96±0.385	72.43±0.778	89.17±0.904	98.58±0.933

In vitro dissolution profile of various formulations studied. From the results of in vitro dissolution studies of sustained release formulations it was observed that the formulation F_1 to F_6, formulation F_6 having a release profile up to 12 hours was selected for formulation of inlay tablet. It was concluded that the drug release from the hydrophilic polymer HPMC $K_{100}M$ shows the better release rate in which the concentration of polymers respect to the drug was 40% w/w. So, as the polymer concentration increases the release time also increases. All the polymers showed the sustained release property. Among both the polymers HPMC $K_{100}M$ shows the release up to 12 hours at higher concentration with other polymer xanthan gum. Among xanthan gum and HPMC K100M, latter was better polymer due to its gel swelling and diffusion mechanism. Different concentrations of polymers were used in the formulation F4, F5, F6. Sustained release was found best with higher concentration of polymer because as the concentration increases, swelling increases and thus drug release rate decreases causing sustained release.

Fig No.21. Comparitive dissolution profile of F1, F2,F3

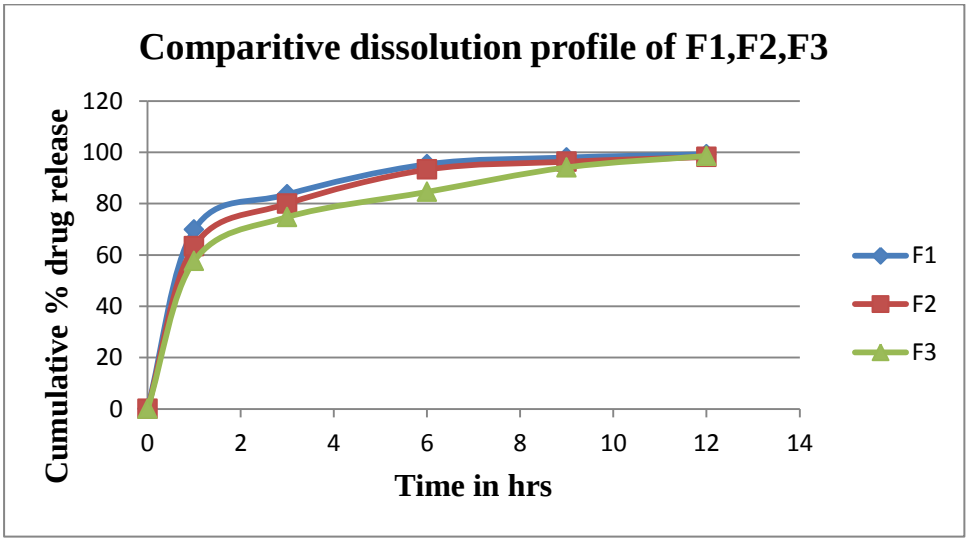


Fig No.22 Comparitive dissolution profile of F4, F5, F6

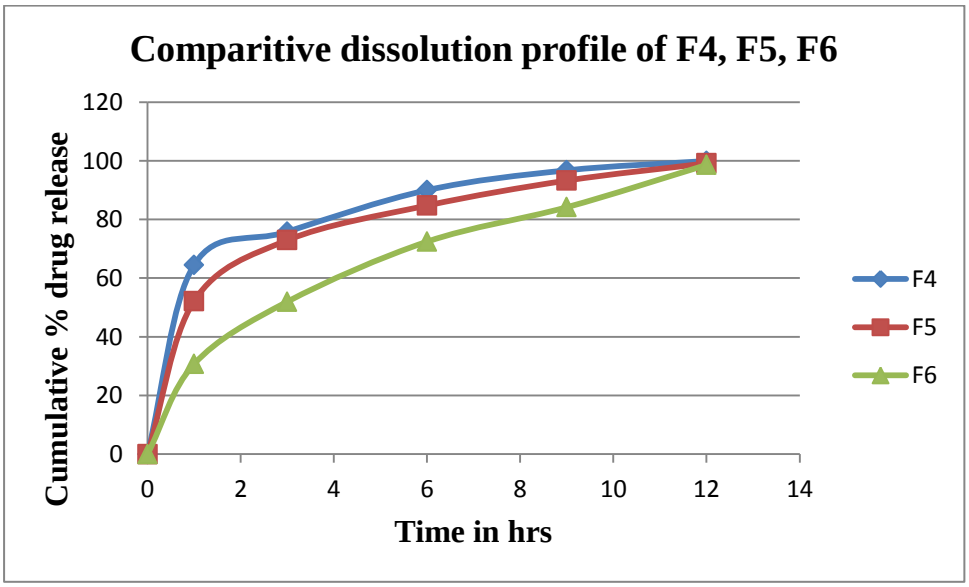
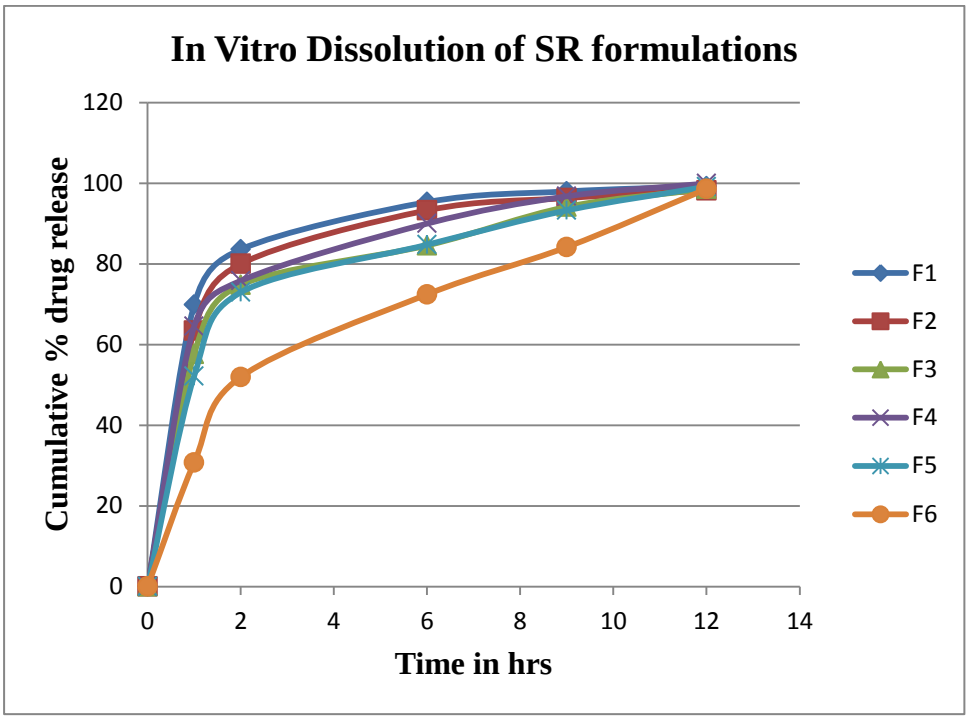


Fig No.23 In Vitro dissolution profile of various SR formulations



8.4. PRE COMPRESSION STUDY FOR IR FORMULATION:

8.4.1. Bulk density:

The bulk density of various powder mixed blends prepared with different superdisintegrants was measured by graduated cylinder. The bulk density was found in the range from 0.52 to 0.55 g/cm^3. The results are presented in Table No.16.

8.4.2. Tapped density:

The tapped density of various powder mixed blends prepared with different superdisintegrants was measured by measuring cylinder. The tapped density was found in the range from 0.60 to 0.63 g/cm^3. The results are presented in Table No.16.

8.4.3. Compressibility index:

A flow property plays an important role in pharmaceuticals especially in tablet formulation because improper flow may cause more weight variation. Values of Carr's Index

(Compressibility) below 15% usually give rise to good flow properties but readings above 25% indicate poor flow properties. The compressibility index of various powder mixed blends prepared with different super disintegrants was calculated using bulk density and tapped density data. It was found in the range 13.50 to 14.20% and hence they exhibit good flow property. The results are given in Table No.16.

8.4.4. Hausner's ratio:

Hausner ratio is an indirect index of ease of powder flow. Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25). The hausner ratio of various powder mixed blends prepared with different superdisintegrants, was calculated by using bulk density and tapped density data. It was found in the range of 1.14 to 1.15 which indicates better flow property. The results are given in Table No.16.

8.4.5. Angle of repose (θ):

The angle of repose of various powder mixed blends prepared with different superdisintegrants was measured by funnel method. Angle of repose was found in the ranges from 22.9^0 to 23.5^0. So, also evidenced with angle of repose that granules have a good flow property. The results are given in Table No.16.

Table No.16: Pre compression study for IR formulation

Formulation	Bulk density* g/cm^3	Tapped density* g/cm^3	Compressibility index* g/cm^3	Hausner's ratio*	Angle of repose*
F_1	0.52±0.013	0.61±0.001	14.20±0.625	1.15±0.018	22.9±0.259
F_2	0.55±0.002	0.60±0.006	13.74±0.829	1.15±0.014	23.5±0.621
F_3	0.53±0.007	0.63±0.003	13.50±0.120	1.14±0.012	23.5±0.860

***** Mean ± SD (n=3)

8.5. POST COMPRESSION OF IR TABLET:

8.5.1. Weight variation:

The theoretical average weight of various formulated tablets was 60mg and weight variation of various formulation are depicted in Table No.17. The percentage deviation of the weight was within 10% as per monograph.

8.5.2. Hardness:

The hardness of various tablet formulation was shown in Table No.17. The hardness of tablet was found in the ranges from 3.06 to 3.5 Kg/cm^2. So, it was the sufficient hardness for tablet coating, transporting and packing.

8.5.3. Thickness:

The thickness of the various tablet formulation was shown in Table No.17. The thickness of the tablet was found in the ranges from 2.91 to 2.94 mm. It was important for packing of tablet and acceptance.

8.5.4. Friability:

The friability of the various tablet formulation was shown in Table No.17. The friability of the tablet was found in the ranges from 0.61 to 0.67%. The values are within limit of the official monograph i.e., not more than 1%.

8.5.5. Disintegration time:

The disintegration time of various tablet formulation was shown in Table No.17. The disintegration time was found to be least for the formulation IR_3.

8.5.6. Drug content:

The content of the various formulations was analyzed by UV spectrometric method. It was very important for the release percentage from the amount present in the tablet. The percentage of drug found in the tablet ranges from 100.27 to 100.38% and was within the limits. The drug content of various formulations was shown in table no.17.

Table No.17: Post compression study of IR Tablet

Formulation	Weight variation*	Hardness* (Kg/cm^2)	Thickness* (mm)	Friability* (%)	Disintegration time* (sec)	%Drug content*
IR_1	100.38±0.7	3.53±0.255	2.91±0.92	0.67±0.329	32±3.719	100.38±0.728
IR_2	100.32±0.6	3.20±0.045	2.98±0.69	0.61±0.441	24±2.281	100.32±0.623
IR_3	100.27±0.7	3.06±0.076	2.94±0.80	0.66±0.019	13±1.005	100.27±0.761

***** Mean ± SD (n=3)

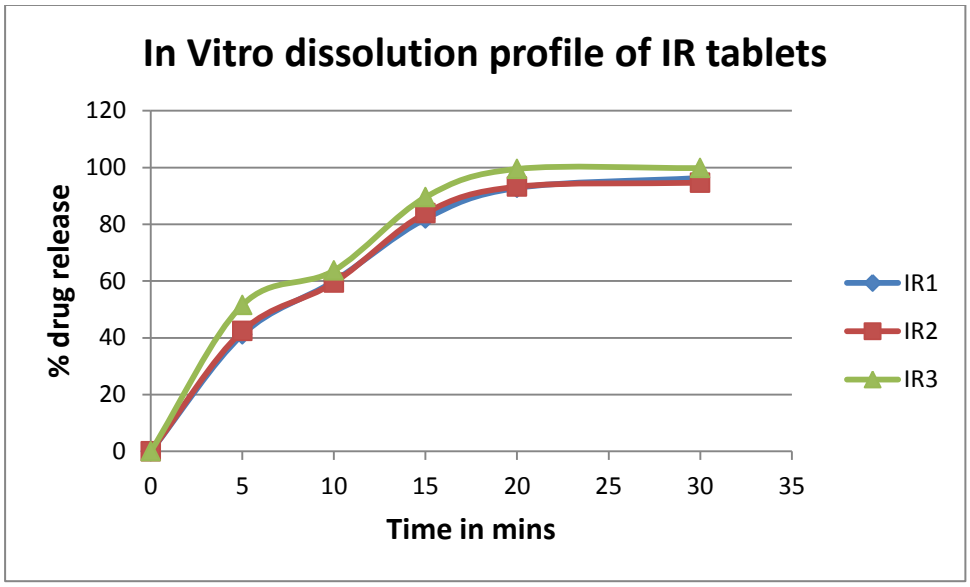
8.5.7. In vitro dissolution release profile and optimization of IR tablet:

In vitro dissolution release profile of various formulations were studied. On comparision of all the formulations, Formulation IR3 released 89% of drug within 15 mins. So Formulation IR3 containing crospovidone was found to be best among all the three formulations, this might be due to its less swelling and greater water uptake tendency compared to other super disintegrants croscarmellose sodium and SSG.

Table No.18: In vitro dissolution profile of IR tablet

Time in min	Formulation		
	IR_1	**IR_2**	**IR_3**
5	41.12±1.07	42.39 ±1.54	51.55±1.92
10	59.95±1.52	59.41±1.41	63.70± 1.40
15	81.93±1.28	83.92±1.79	89.54± 1.71
20	92.81±1.02	93.23±1.83	99.48± 1.29
30	96.31±1.53	94.64±1.62	99.79±1.22

Fig No.24 In Vitro dissolution profile of various IR formulations



8.6. FORMULATION AND EVALUATION OF INLAY TABLETS:

From the results of in vitro dissolution studies of IR and SR formulations

Table No.19 : Formulation for inlay tablets (Wt in mg)

Sustained release layer (F)	Per tablet (mg)	Immediate release layer (F)	Per tablet (mg)
Metfromin HCl	500	Gliclazide	40
HPMC $K_{100}M$	200	MCCP pH 102	12
MCCP pH102	40	Crospovidone	7
Iso propyl alcohol	q.s	Mg stearate	0.5
Talc	5	Talc	0.5
Mg stearate	5	Indigo blue	q.s

Table No.20: Evaluation of inlay tablets

Parameters	Results
Uniformity of weight*(mg)	810.62±5.49
Tablet thickness*(mm)	6.952±0.041
Hardness*(kg/cm^2)	6.73±0.416
Friability*(%)	0.042±0.022
Disintegration time*(sec)	2.83±0.065

*****mean ± SD (n=3)

All the parameters shown in table complies with the official monograph

8.6.1. Swelling and erosion behaviour of inlay tablets:

Table No.21: Swelling and erosion behaviour of inlay tablets

Time in hours	% of swelling	% of erosion
0	0	**0**
1	6.75±0.086	2.086±0.261
2	7.41±0.045	3.124±0.167
3	9.34±0.027	3.726±0.048
5	10.92±0.114	4.461±0.087
7	11.29±0.223	4.519±0.097
9	13.87±0.074	4.702±0.056
12	15.63±0.029	4.873±0.049

The results showed in Table No.21 says that the SR tablets maintained their integrity gave increased swelling through the course of study. Thus the extent of swelling increases with amount of swellable polymer.

8.6.2. Drug content:

Drug content of inlay tablet containing metformin HCl and gliclazide was done by two steps. The results were shown in Table No.22 which were within the limits.

Table No.22: Drug content of the inlay tablet

Inlay tablet	% Drug content
Metformin hydrochloride	99.43±0.52
Gliclazide	100.29±0.48

8.6.3. In vitro release profile of inlay tablet:

Data obtained from the dissolution profile of SR and IR layer was shown in table no.23.

Table No.23: In vitro dissolution profile of SR and IR layer*

Immediate release layer		Sustained release layer	
Time in min	**Cumulative % of drug release**	**Time in hours**	**Cumulative % of drug release**
5	50.52±1.83	1	28.35±0.37
10	65.30± 1.50	3	48.53±0.61
15	88.27± 1.46	6	69.28±0.52
20	99.04± 1.71	9	88.61±0.46
30	99.64±1.42	12	98.42±0.36

***mean ± SD (n=6)

8.6.4. Kinetic study of inlay tablet:

Data obtained from in vitro release of metformin hydrochloride from the inlay tablets were fitted in various kinetic models and results are tabulated in the Table No.24.

Table No.24: Data for various kinetic models

Time (hours)	% cum. Drug release	% cum drug remaining	Log % cum drug remaining	Square root of time	Log time	Log % cum. Drug release	Cube root of % drug remaining
0	0	100	2.000	0	0	0	4.641
1	28.35	71.65	1.855	1	0	1.452	4.153
3	48.53	51.47	1.711	1.732	0.477	1.686	3.719
6	69.28	30.72	1.487	2.449	0.778	1.840	3.131
9	88.61	12.39	1.214	3	0.954	1.922	2.540
12	98.42	1.58	0.198	3.464	1.079	1.993	1.164

Fig No.25 Zero order kinetics of SR

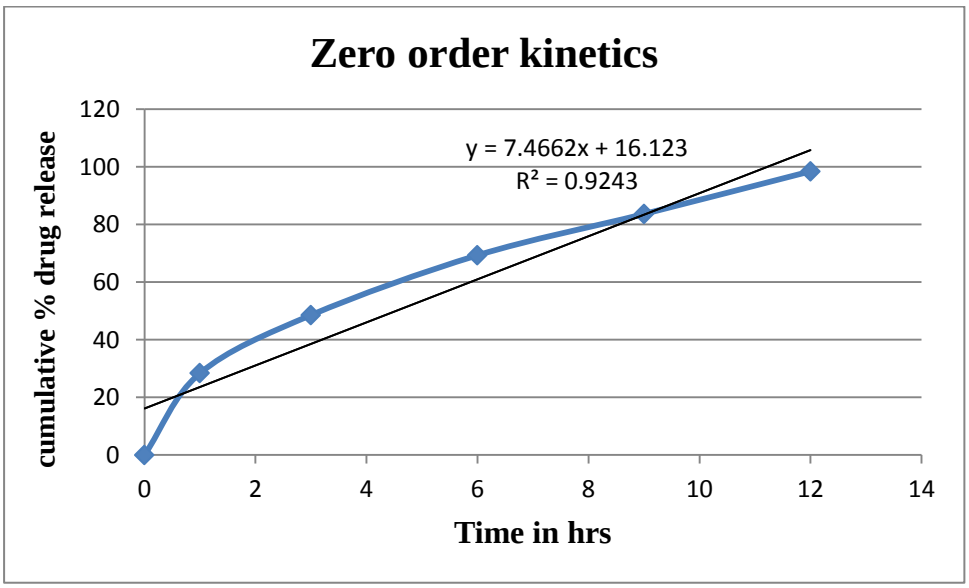


Fig No.26 First order kinetics of SR

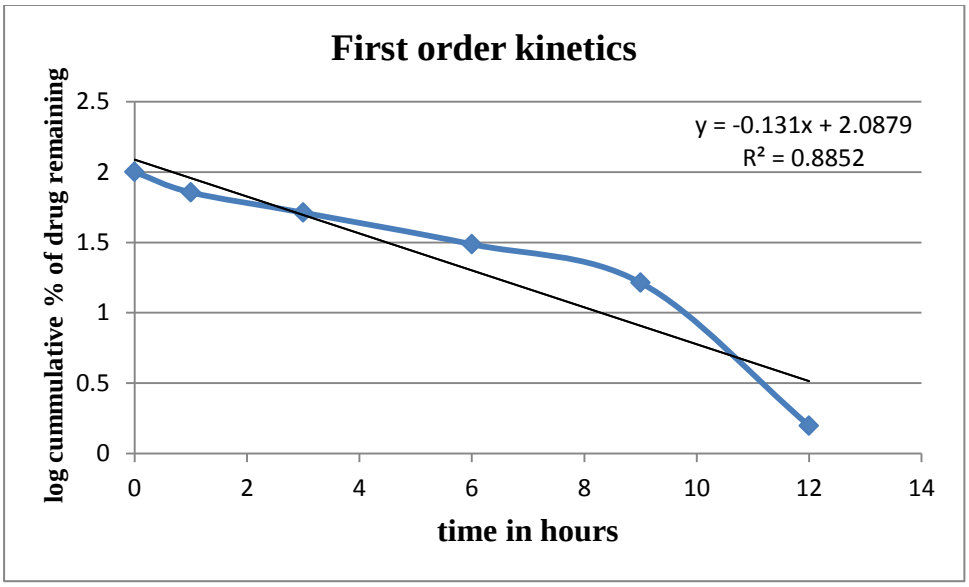


Fig No.27 Higuchi diffusion kinetics of SR

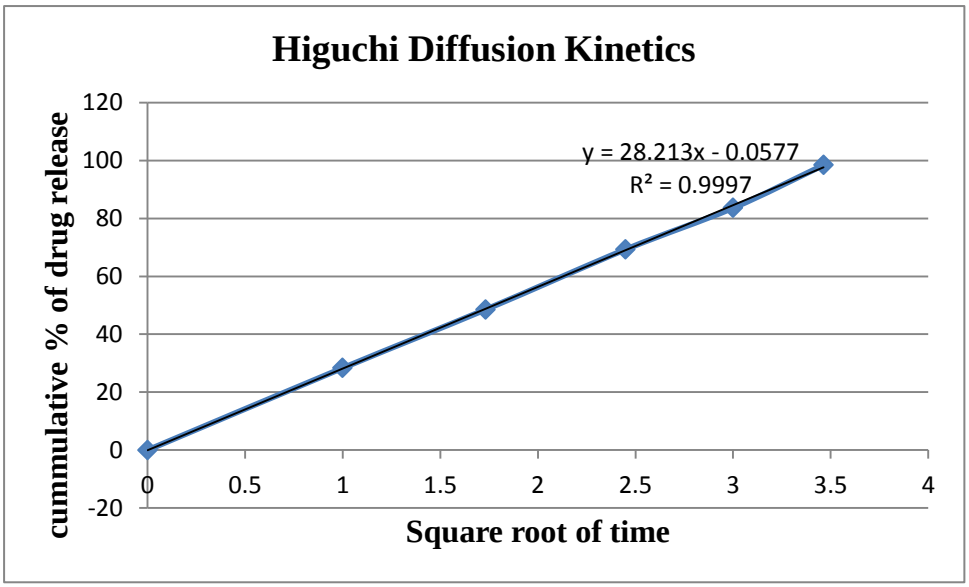


Fig No.28 Hixson Crowell equation of SR

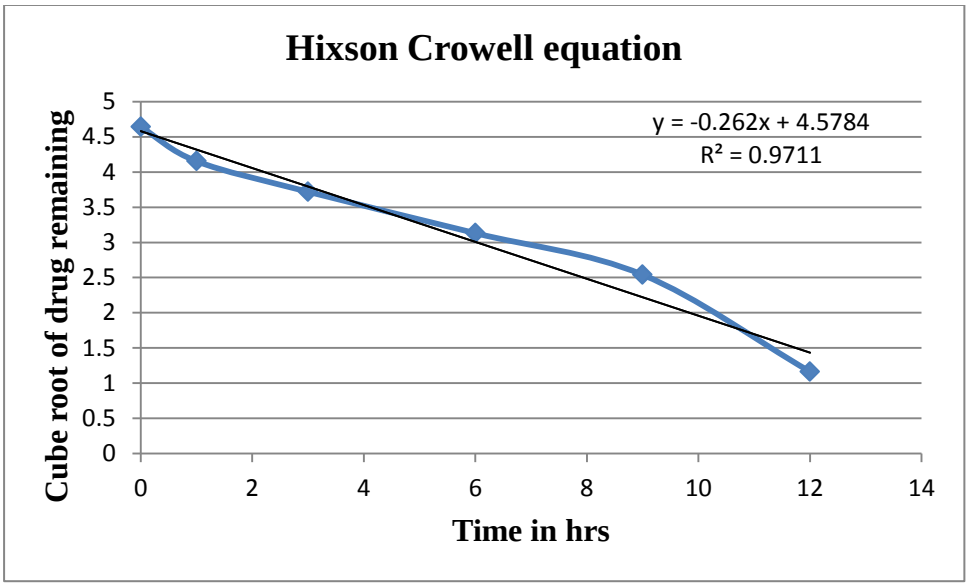
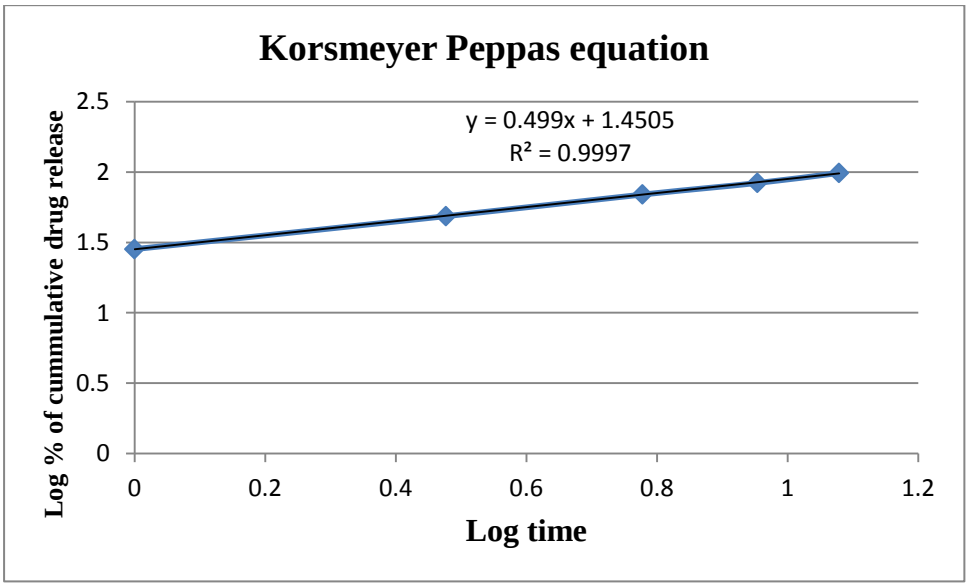


Fig No.29 Korsmeyer Peppas equation of SR



	Regression coefficient
Zero order	0.9243
First otder	0.8852
Higuchi's square root equation	0.9997
Hixson srowell cube root equation	0.9711
Korsmeyer peppas equation	0.9997

The drug release data obtained was extrapolated by Zero order, First order, Higuchi square root equation, Hixson crowell cube root equation and Korsmeyer peppas equation to know drug release mechanism from this formulation.

Regression coefficient (R^2) showed good linearity with Zero order equation (0.9243) when compared to First order equation (0.8852) indicating that drug release is independent of concentration of the drug.

In vitro release profile could be best expressed by Higuchi square root equation as plots showed highest linearity (0.9997) when compared to Hixson crowell cube root equation (0.9711). It confers that drugs are released by diffusion.

To confirm diffusion mechanism, the data was fitted to Korsmeyer peppas equation. Formulation showed good linearity with diffusion exponent(n) value 0.4999 indicating that diffusion was predominant mechanism of drug release fron this formulation indicating that drug release mechanism was Non fickian or anomalous release ($0.45<n<0.89$). It can be inferred that release was dependant both on drug diffusion and polymer relaxation, which appears to indicate a coupling of diffusion and erosion mechanisms so called anomalous diffusion.

8.6.5. Determination of drug release mechanism of immediate release layer from optimized inlay tablets:

Table No.25: Data for various kinetic models

Time in min	% Drug release	% To be released	Log % drug remaining
0	0	100	2.000
5	50.52	49.48	1.694
10	65.30	34.7	1.540
15	88.27	11.73	1.069
20	99.04	0.96	-0.017
30	99.64	0.36	-0.443

Fig No.30 First order kinetics of IR

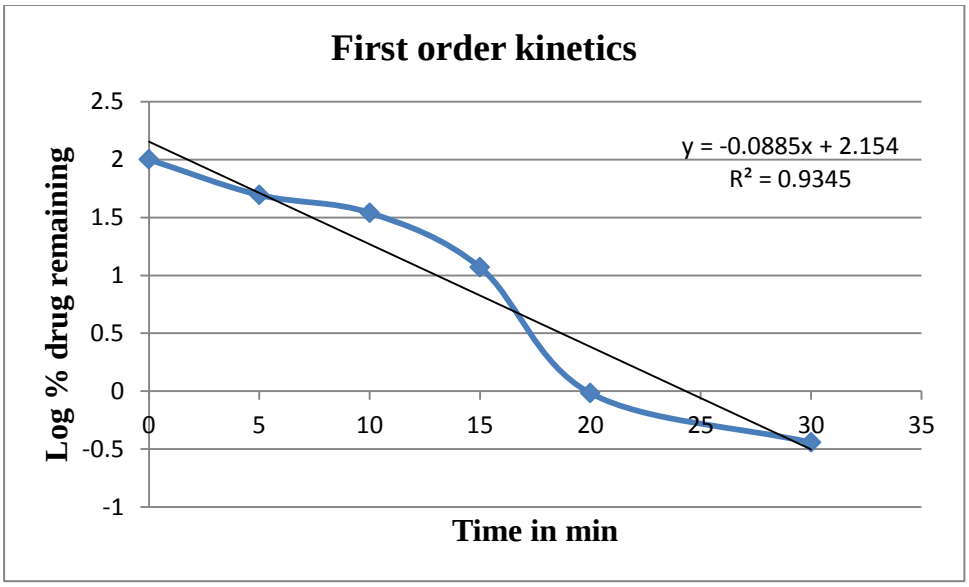
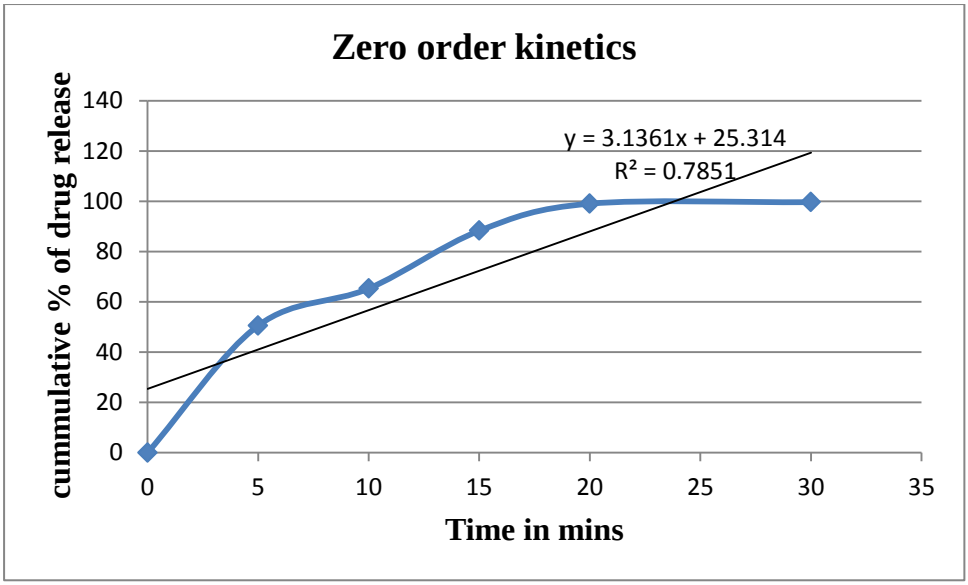


Fig No.31 Zero order kinetics of IR



From the above graphs it was concluded that gliclazide was following first order of release with regression value of 0.9345.

8.6.6. Stability study:

The optimised inlay tablets were subjected to stability studies and results were tabulated in Table No.26 and Table No.29.

Table No.26: Stability study at 40˚C/75% RH

Parameters	1st month		2nd month		3rd month	
	RT	40˚C	RT	40˚C	RT	40˚C
Uniformity of weight**(mg)	810.72±1.4	810.67±1.2	810.64±1.3	810.66±1.8	810.62±1.5	810.63±1.4
Thickness*(mm)	6.952±0.09	6.954±0.09	6.957±0.07	0.950±0.09	0.955±0.09	0.951±0.08
Hardness*(kg/cm^2)	6.74±0.693	6.74±0.682	6.74±0.684	6.74±0.697	6.74±0.691	6.74±0.688
D.time*(sec)	2.77±0.261	2.76±0.285	2.77±0.229	2.77±0.249	2.77±0.237	2.77±0.289
Friability*(%)	0.16±0.232	0.16±0.325	0.17±0.211	0.16±0.281	0.16±0.261	0.16±0.247

Table No.27 Assay and dissolution profile of inlay tablet at stability study at 40˚C/75% RH

Intervals in months	Drug	% drug content*		% cumulative release*	
		RT	40˚C	RT	40˚C
1st month	Metformin HCl	100.28±0.79	100.45±0.67	97.97±0.48	97.62±0.82
	Gliclazide	100.16±0.89	100.28±0.78	98.42±0.22	97.32±0.19
2nd month	Metformin HCl	100.24±0.74	100.38±0.59	97.91±0.72	97.51±0.42
	Gliclazide	100.15±0.68	100.22±0.64	97.57±0.59	96.37±0.48
3rd month	Metformin HCl	100.22±0.71	100.36±0.55	97.83±0.28	97.49±0.53
	Gliclazide	100.14±0.66	100.20±0.62	98.72±0.39	96.24±0.95

10. SUMMARY AND CONCLUSION

The present research endeavour is directed towards the development of inlay tablets of Metformin HCl as sustained release and Gliclazide as immediate release.

All the formulations were evaluated for physical characteristics, disintegration, *In Vitro* dissolution study and stability study. Following conclusions have been made from the present study.

- The possibility of drug excipients interaction was investigated by FTIR. The physical characteristics of all the blended formulations were satisfactory.
- The prepared tablets of sustained release and immediate release were evaluated for assay, weight variation, hardness, thickness, friability and disintegration time and results were found to be within official limits.
- The disintegration studies showed that immediate release formulation IR_3 prepared by direct compression technique using crospovidone was best disintegrating within 13 sec.
- The *In Vitro* dissolution studies were performed for all the IR formulations. Among all the formulations, IR_3 containing crospovidine showed fastest release i.e., 95.48% of drug within 10mins.
- *In Vitro* dissolution study of SR formulations was performed and release profile of formulation F6 containing 40% concentration of HPMC K100 M was best when compared to other five formulations.
- Inlay tablet formulation was prepared using optimum formulation of sustained release granules and immediate release granules. Initially Metformin HCl granules were filled in the die cavity, over that immediate release tablet was placed and then compressed finally to get an inlay tablet.
- The inlay tablets evaluated for assay, weight variation, hardness, thickness, friability and disintegration time and the results were found to be within the official limits.
- The dissolution data of the optimized batch was subjected to study the *In Vitro* release kinetics. The results showed that the IR layer of inlay tablet formulation followed the first order release kinetics and the drug release kinetics of SR layer of inlay tablet formulation corresponds best to Higuchi's model and drug release mechanism as per n value of Korsmeyer and Peppas model appeared to be a complex mechanism of swelling, diffusion and erosion with zero order release kinetics.

- The stability study was conducted for 3 months under room temperature and 45^0C/75% RH. Finally after the duration, the product was analysed for physical appearance, disintegration time, dissolution study and assay. The results obtained were found to be within the specification limits.

Thus from the results of the present study it was concluded that anti-diabetic drugs with different mechanism of action formulated as inlay tablet improved glycemic control by releasing drug up to 12 hours and there by reducing frequency of administration and improving patient compliance.

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